Abstract

PCSK1 is a serine protease involved in the proteolytic processing of a variety of protein precursors mainly neuropeptides and prohormones. In 1991, PC1/3; also known as PCSK1, PC1, PC3, and SPC3 was identified at the same time by two laboratories separately. The human and mouse PCSK1 genes are localized on chromosomes 5 and 13, respectively. The cleavage of these protein precursors is required for the mediation of their functions including the regulation of glucose homeostasis and food intake. The PCSK1 substrates that regulate these functions include proinsulin, proglucagon, proghrelin and proopiomelanocortin and others. PCSK1 polymorphisms were associated with risk of obesity and with various endocrine disorders. PCSK1 is also involved in the regulation of macrophage activation and cytokine secretion. The inhibition of PCSK1 activity was proposed to reverse the macrophage phenotype from an M2-like to an M1-like phenotype. PCSK1 is highly expressed in breast cancers and in neuroendocrine tumors including carcinoïd tumors. The expression of this protease at the RNA and protein levels is also increased in liver colorectal metastasis, suggesting PCSK1 activity in tumorigenesis, however the evidence of PCSK1 roles in these cancers and probably others remain to be defined.

Keywords
PCSK1, PC1, endocrine disorders, cancer, chromosome 5.

Identity

Other names
NEC1, PC1, PC3, SPC3

HGNC (Hugo)
PCSK1

Location
5q15

Location (base pair)
Starts at 95726040 and ends at 95768985 bp from pter (according to hg19-Feb_2009)

DNA/RNA

Figure 1: Genomic organization of PCSK1.
PCSK1 (proprotein convertase subtilisin/kexin type 1)

**Description**
The PCSK1 gene is located on chromosome 5q15-21 in humans, and chromosome 13c in the mouse (Seidah NG et al. 1991a, Seidah NG et al. 1991b). The promoter of this gene contains cAMP-response elements (CRE-1 and CRE-2). Transcription factors such as cAMP-responsive element-binding protein 1 (CREB1) and Activating Transcription Factor 1 (ATF1) that can transactivate the PCSK1 promoter (Jansen E et al, 1997, Espinosa VP et al, 2008).

**Transcription**
The DNA sequence of PCSK1 contains 14 exons and the transcript length of 5068 bps is translated to a 753 residues protein. 4 spliced variants of PCSK1 are identified (splice variants) that code for 3 protein isoforms of 753 aa, 706 aa and 157 aa in length, respectively (M_000439, NM_001177875).

**Protein**
Figure 2: Diagram representing the protein structure of PCSK1. PCSK1 is a multi-domain serine proteinase consisting of a signal peptide followed by prosegment, catalytic, middle, and cytoplasmic domain. The P domain just after the catalytic domain is required for the stabilization of the catalytic domain. The C-terminal domain is involved in the routing of PC1/3 to the secretory granules.

**Description**
PCSK1 is the third member of the proprotein convertase Subtilisin/Kexin-like family that was cloned from mammalian organisms, after furin and PC2 (Seidah NG et al. 1991, Smeekens SP et al, 1991, reviewed in Scamuffa N et al, 2006). The domain structure of PCSK1 precursor consists of four domains that include a prodomain (or prosegment), a catalytic domain, a P domain, and a carboxy-terminal domain (Figure 2). The propeptide domain is essential for the appropriate protein folding and exit from the endoplasmic reticulum (ER) of PCSK1 (Creemers JW1 et al, 1995). The catalytic domain is highly conserved among various species. Similar to the other members of the subtilisin superfamily the amino acids Asp, His, and Ser form the catalytic triad. The P domain presents a key role in the regulation of the PCSK1 activity through calcium and pH modulation (Zhou A1 et al, 1998). The carboxy-terminal domain is mainly involved in PCSK1 sorting into secretory granules (Dikeakos JD et al. 2009).

After the production of PCSK1 preproform in the endoplasmic reticulum and removal of its signal peptide, the 94kDa precursor of PCSK1 activation occurs after both N-and C-terminal domains cleavages. The 94kDa precursor undergoes an initial autocatalytic processing of its prosegment (prodomain). After protein scaffold and N-glycosylation, proPCSK1 exits the ER and sorts to the trans-Golgi network. In the early compartment, proPCSK1 is sulfated on its sugar residues. Lately during progression to the mildly acidic environment, an autocatalytic cleavage occurs to remove the prodomain and generates a 87kDa active PCSK1 form (reviewed in Ramos-Molina B et al., 2016 and Stijnen P et al 2016). The cleavage of proPCSK1 that generates the 87 kDa PCSK1 is calcium-independent and occurs at a neutral pH. PCSK1 is sorted after to immature secretory granules where is activated by a cleavages at the C-terminal area and generates the 74 and 66kDa active forms. The active forms are than accumulated in dense-core secretory granules prior secretion.

**Expression**
PCSK1 is expressed in the neuroendocrine system such as brain, adrenal glands and in endocrine cells of the small intestine (reviewed in Ramos-Molina B et al., 2016 and Stijnen P et al 2016). Weak expression of PCSK1 is detected in adipocytes, α-cells of the pancreatic islets and certain types of immune cells. In brain, PC1 is mainly expressed in the hypothalamus (Dong W et al., 1997), but it is also found in cerebral cortex (Figure 3), hippocampus, and cerebellum (Billova S1, ET AL., 2007, Schäfer MK1, et al 1993). PC1/3 is also expressed in the adrenal medulla, pituitary, thyroid gland (Scopsi L et al. 1995, Day R ET AL 1992), endocrine pancreas (β-cells), liver and small intestine; including L and K cells (Tanaka S ET AL 1996). At low levels, PC1/3 was also detected in adipocytes (Min SYet al, 2016), in pancreatic islets (Itoh Y1, et al 1996), and in certain types of immune cells (LaMendolaet al 1997, Vindrola O et al 1994).
PCSK1 (proprotein convertase subtilisin/kexin type 1)

**Localisation**
In neuroendocrine cells, PCSK1 is mainly localized to the secretion granules and traffics within the regulated secretory pathway (Hornby PJ et al 1993, Malide D et al 1995). In macrophages PC1/3 is retained at the TGN as a pool that traffics to LAMP-related vesicles. PC1 vesicles are mostly detected during macrophages activation (Gagnon H et al, 2013).

**Example of PCSK1 expression in the cerebral cortex and liver.** Shown are overviews of stained tissues (circle) with high magnification of representative region (square). Adapted from Protein Atlas database.

**Function**
PCSK1 cleaves protein precursors at the consensus motif (K/R)-Xn-(K/R), with n=0, 2, 4 or 6, and X=any amino acids except Cys, to release mature proteins. PCSK1 favors cleavage after K/R motif, but is also able to cleave after other dibasic residues. PCSK1 often collaborates with PCSK2 to cleave substrates, such as neuropeptides and peptide hormones and its activity can be inhibited by the endogenous inhibitor proSAAS. PC1/3 gene disruption results in various developmental abnormalities (reviewed in Ramos-Molina B et al, 2016 and Stijnen P et al 2016) and PC1/3 null mice exhibit growth retardation (reviewed in Scamuffa N et al, 2006). The adult mutant mice are 60% of the normal size and show similarities with mice having mutant growth hormone releasing hormone (GHRH) receptor (GHRHR). Further analysis indicated that insulin-like growth factor-1 (IGF1) and GHRH levels were significantly decreased in these mice; that may explain the observed growth retardation. PCSK1 null mice process normally pituitary POMC to ACTH and have normal levels of blood corticosterone. Like PCSK2 null mice, PCSK1 null mice also develop hyperproinsulinemia. These mice maintain normal glucose (Glc) tolerance in response to injection of glucose, suggesting that their hyperproinsulinemia does not impair their glucose homeostasis. Previously, Jackson et al. (reviewed in Scamuffa N et al, 2006) reported a human case of...
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PC1/3 deficiency. The latter is due to PCSK1 gene mutation that prevents activation and secretion of proPC1/3 from the endoplasmic reticulum. The patient showed neonatal obesity. Subsequent studies revealed the presence of various endocrine defects, including the presence of very high circulating levels of proinsulin and multiple forms of partially processed POMC [ACTH precursors intermediate], low-serum estradiol, follicle-stimulating hormone, and LH. In 2003, another PCSK1 deficiency female subject was reported. In addition to the shared phenotypes with the previous subject, this female infant presented severe diarrhea, which started on the third postnatal day. Metabolic studies revealed a defect in the absorption of monosaccharides and fat, revealing the role of PC1/3 in the small intestinal absorptive function. Although the phenotypes of the PCSK1 null mice differ from those observed in these patients (PCSK1 null mice are not obese), the findings confirmed the importance of PCSK1 as a key neuroendocrine convertase (reviewed in Ramos-Molina B et al., 2016 and Stijnen P et al 2016).

**Homology**

An important paralog of this gene is PCSK2. Analysis of PCSK1 structure revealed that PCSK1 catalytic domain present a low percentage of homology with those of the other PCs (only 39% between PCSK1 and FURIN). The PCSK1 prodomain is formed by 83 residues and is highly conserved between orthologs (~80% of sequence identity), although is not well conserved among paralogs of the convertase family (~30-40%). The catalytic domain of PC1/3 is formed by 343 residues and is the most conserved region among proproteine convertases family members, with 50-60% sequence similarity. The P domain is a well-conserved region in PCs of approximately 150 residues and the Arg526-, Arg-Gly-Asp529 (RRGD motif) is crucial for proper proPC1/3 processing and sorting to the secretory granules (reviewed in Ramos-Molina B et al., 2016 and Stijnen P et al 2016). The C-terminus of PCSK1 with 159 aa is involved in the sorting processes to the dense core secretory granules, as well as in PCSK1 activity and stability (reviewed in Ramos-Molina B et al., 2016 and Stijnen P et al 2016).

**Mutations**

**Germinal**

Various mutations were reported for human PCSK1 gene and were associated with various syndromes including obesity, malabsorptive diarrhea, hypogonadotropic hypogonadism, altered thyroid and adrenal function, and impaired regulation of plasma glucose levels (reviewed in Ramos-Molina B et al., 2016 and Stijnen P et al 2016).

**Implicated in**

**Breast cancer**


**Colon cancer and colon cancer metastasis**

PC1 expression and protein cleavage profiles are altered in colon cancer and liver colorectal metastasis, compared to unaffected and normal liver. Active PCSK1 protein is overexpressed in these tumors and was found to correlate with the mRNA profiles (Tzimas G, et al 2005).

**Neuroendocrine tumors**

High expression of PCSK1 is reported for neural and/or endocrine phenotype (Takumi I et al 1998, Jin L et al. 1999, Kajiwara H et al. 1999). However the role and prognostic value of PCSK1 in endocrine-related cancers is still unclear.

**Endocrine disorders**

PCSK1 deficiency is a very rare genetic disorder, few patient cases have been reported. In human, the lack of PCSK1 was reported to be associated with several cases of hypogonadotropic and/or hypogonadism (O’Rahilly et al, 1995). Several patients showed low serum estradiol, FSH, and LH (Jackson R et al. 1997, Martèn MG et al. 2013, Bandsma RH, et al 2013, Wilschanski ET AL 2014, Solorzano-Vargas RS et al 2013).

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