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Gene Section

Review

PCSK1 (proprotein convertase subtilisin/kexin type 1)

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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 carcinoid 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

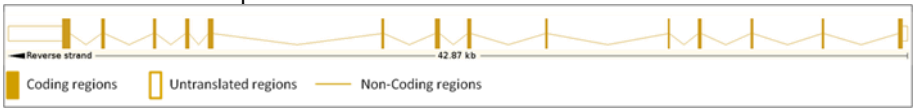


Figure 1: Genomic organization of PCSK1.

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 PCSK1contains 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

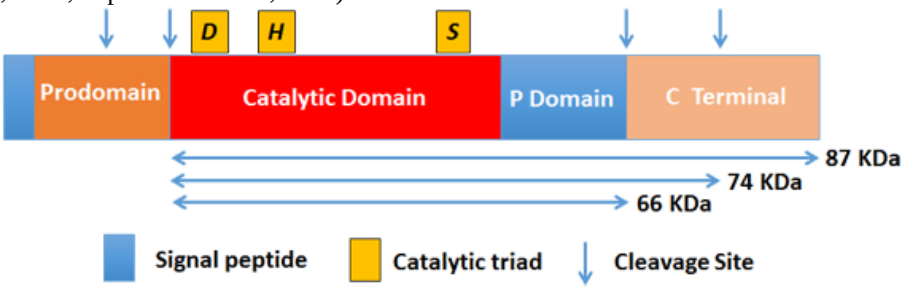


Figure 2: Diagram representing the protein structure of PCSK1. PCSK1 is a multi-domain serine proteinase consisting of a signal peptide followed by prosegment, catalytic, middle, and cytoplasmic domain. The P domain just after the catalytic domain is required for the stabilization of the catalytic domain. 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

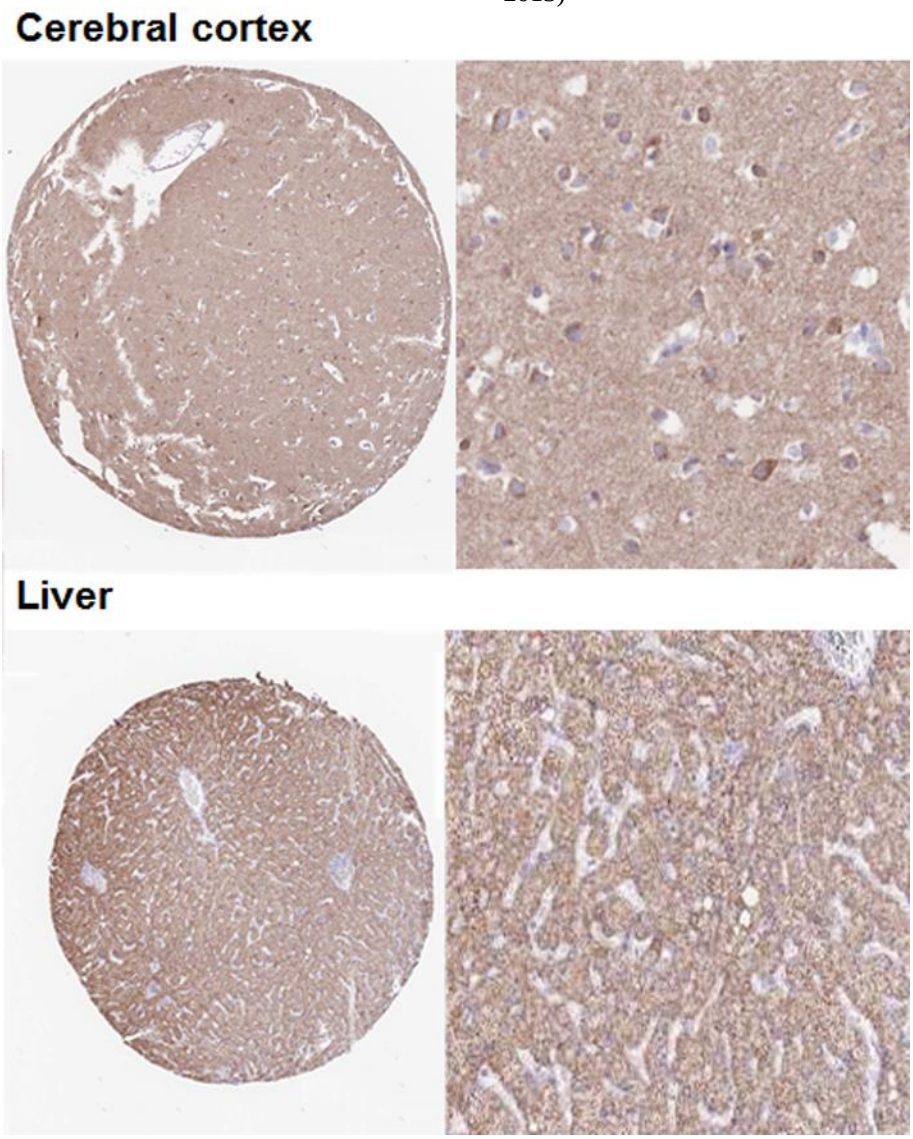
accumulated in dense-core secretory granules prior secretion.

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).

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 vesicules 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

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 Arg^{526}-Arg-Gly-Asp^{529} (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

PC1 is highly elevated in human breast carcinomas (Cheng et al.1997). Stable expression of PC1 in human breast cancer cells MCF-7 altered their growth rate and response to estrogen and anti-estrogen treatments (Cheng et al. 2001). The use of transgenic mouse model revealed that PCSK1 expression promote normal and neoplastic mammary development and growth (Blanchard A et al 2009).

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).

References

Bandsma RH, Sokollik C, Chami R, Cutz E, Brubaker PL, Hamilton JK, Perlman K, Zlotkin S, Sigalet DL, Sherman PM, Martin MG, Avitzur Y. From diarrhea to obesity in prohormone convertase 1/3 deficiency: age-dependent clinical, pathologic, and enteroendocrine characteristics. J Clin Gastroenterol. 2013 Nov-Dec;47(10):834-43

Billova S, Galanopoulou AS, Seidah NG, Qiu X, Kumar U. Immunohistochemical expression and colocalization of somatostatin, carboxypeptidase-E and prohormone convertases 1 and 2 in rat brain. Neuroscience. 2007 Jun 29;147(2):403-18

Blanchard A, Iwasiow B, Yarmill A, Fresnosa A, Silha J, Myal Y, Murphy LC, Chrétien M, Seidah N, Shiu RP. Targeted production of proprotein convertase PC1 enhances mammary development and tumorigenesis in transgenic mice. Can J Physiol Pharmacol. 2009 Oct;87(10):831-8

Cheng M, Watson PH, Paterson JA, Seidah N, Chrétien M, Shiu RP. Pro-protein convertase gene expression in human breast cancer. Int J Cancer. 1997 Jun 11;71(6):966-71

Cheng M, Xu N, Iwasiow B, Seidah N, Chrétien M, Shiu RP. Elevated expression of proprotein convertases alters breast

cancer cell growth in response to estrogen and tamoxifen. J Mol Endocrinol. 2001 Apr;26(2):95-105

Creemers JW, Vey M, Schäfer W, Ayoubi TA, Roebroek AJ, Klenk HD, Garten W, Van de Ven WJ. Endoproteolytic cleavage of its propeptide is a prerequisite for efficient transport of furin out of the endoplasmic reticulum. J Biol Chem. 1995 Feb 10;270(6):2695-702

Day R, Schafer MK, Watson SJ, Chrétien M, Seidah NG. Distribution and regulation of the prohormone convertases PC1 and PC2 in the rat pituitary. Mol Endocrinol. 1992 Mar;6(3):485-97

Dikeakos JD, Di Lello P, Lacombe MJ, Ghirlando R, Legault P, Reudelhuber TL, Omichinski JG. Functional and structural characterization of a dense core secretory granule sorting domain from the PC1/3 protease. Proc Natl Acad Sci U S A. 2009 May 5;106(18):7408-13

Dong W, Seidel B, Marcinkiewicz M, Chrétien M, Seidah NG, Day R. Cellular localization of the prohormone convertases in the hypothalamic paraventricular and supraoptic nuclei: selective regulation of PC1 in corticotrophin-releasing hormone parvocellular neurons mediated by glucocorticoids. J Neurosci. 1997 Jan 15;17(2):563-75

Duhamel M, Rodet F, Delhem N, Vanden Abeele F, Kobeissy F, Nataf S, Pays L, Desjardins R, Gagnon H, Wisztorski M, Fournier I, Day R, Salzet M. Molecular Consequences of Proprotein Convertase 1/3 (PC1/3) Inhibition in Macrophages for Application to Cancer Immunotherapy: A Proteomic Study. Mol Cell Proteomics. 2015 Nov;14(11):2857-77

Espinosa VP, Liu Y, Ferrini M, Anghel A, Nie Y, Tripathi PV, Porche R, Jansen E, Stuart RC, Nillni EA, Lutfy K, Friedman TC. Differential regulation of prohormone convertase 1/3, prohormone convertase 2 and phosphorylated cyclic-AMP-response element binding protein by short-term and long-term morphine treatment: implications for understanding the "switch" to opiate addiction. Neuroscience. 2008 Oct 15;156(3):788-99

Gagnon H, Refaie S, Gagnon S, Desjardins R, Salzet M, Day R. Proprotein convertase 1/3 (PC1/3) in the rat alveolar macrophage cell line NR8383: localization, trafficking and effects on cytokine secretion. PLoS One. 2013;8(4):e61557

Hornby PJ, Rosenthal SD, Mathis JP, Vindrola O, Lindberg I. Immunocytochemical localization of the neuropeptide-synthesizing enzyme PC1 in AtT-20 cells. Neuroendocrinology. 1993 Nov;58(5):555-63

Itoh Y, Tanaka S, Takekoshi S, Itoh J, Osamura RY. Prohormone convertases (PC1/3 and PC2) in rat and human pancreas and islet cell tumors: subcellular immunohistochemical analysis. Pathol Int. 1996 Oct;46(10):726-37

Jackson RS, Creemers JW, Ohagi S, Raffin-Sanson ML, Sanders L, Montague CT, Hutton JC, O'Rahilly S. Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. Nat Genet. 1997 Jul;16(3):303-6

Jansen E, Ayoubi TA, Meulemans SM, Van de Ven WJ. Cell type-specific protein-DNA interactions at the cAMP response elements of the prohormone convertase 1 promoter. Evidence for additional transactivators distinct from CREB/ATF family members. J Biol Chem. 1997 Jan 24;272(4):2500-8

Jin L, Kulig E, Qian X, Scheithauer BW, Young WF Jr, Davis DH, Seidah NG, Chretien M, Lloyd RV. Distribution and regulation of proconvertases PC1 and PC2 in human pituitary adenomas. Pituitary. 1999 May;1(3-4):187-95

Kajiwara H, Itoh Y, Itoh J, Yasuda M, Osamura RY. Immunohistochemical expressions of prohormone convertase (PC)1/3 and PC2 in carcinoids of various organs. Tokai J Exp Clin Med. 1999 Apr;24(1):13-20

LaMendola J, Martin SK, Steiner DF. Expression of PC3, carboxypeptidase E and enkephalin in human monocyte-derived macrophages as a tool for genetic studies. FEBS Lett. 1997 Mar 3;404(1):19-22

Malide D, Seidah NG, Chrétien M, Bendayan M. Electron microscopic immunocytochemical evidence for the involvement of the convertases PC1 and PC2 in the processing of proinsulin in pancreatic beta-cells. J Histochem Cytochem. 1995 Jan;43(1):11-9

Martín MG, Lindberg I, Solorzano-Vargas RS, Wang J, Avitzur Y, Bandsma R, Sokollik C, Lawrence S, Pickett LA, Chen Z, Egritas O, Dalgic B, Albornoz V, de Ridder L, Hulst J, Gok F, Aydoğan A, Al-Hussaini A, Gok DE, Yourshaw M, Wu SV, Cortina G, Stanford S, Georgia S. Congenital proprotein convertase 1/3 deficiency causes malabsorptive diarrhea and other endocrinopathies in a pediatric cohort. Gastroenterology. 2013 Jul;145(1):138-148

Min SY, Kady J, Nam M, Rojas-Rodriguez R, Berkenwald A, Kim JH, Noh HL, Kim JK, Cooper MP, Fitzgibbons T, Brehm MA, Corvera S. Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. Nat Med. 2016 Mar;22(3):312-8

O'Rahilly S, Gray H, Humphreys PJ, Krook A, Polonsky KS, White A, Gibson S, Taylor K, Carr C. Brief report: impaired processing of prohormones associated with abnormalities of glucose homeostasis and adrenal function. N Engl J Med. 1995 Nov 23;333(21):1386-90

Ramos-Molina B, Martin MG, Lindberg I. PCSK1 Variants and Human Obesity. Prog Mol Biol Transl Sci. 2016;140:47-74

Scamuffa N, Calvo F, Chrétien M, Seidah NG, Khatib AM. Proprotein convertases: lessons from knockouts. FASEB J. 2006 Oct;20(12):1954-63

Schäfer MK, Day R, Cullinan WE, Chrétien M, Seidah NG, Watson SJ. Gene expression of prohormone and proprotein convertases in the rat CNS: a comparative in situ hybridization analysis J Neurosci 1993 Mar;13(3):1258-79

Scopsi L, Gullo M, Rilke F, Martin S, Steiner DF. Proprotein convertases (PC1/PC3 and PC2) in normal and neoplastic human tissues: their use as markers of neuroendocrine differentiation J Clin Endocrinol Metab 1995 Jan;80(1):294-301

Seidah NG, Mattei MG, Gaspar L, Benjannet S, Mbikay M, Chrétien M. Chromosomal assignments of the genes for neuroendocrine convertase PC1 (NEC1) to human 5q15-21, neuroendocrine convertase PC2 (NEC2) to human 20p11 1-11 2, and furin (mouse 7[D1-E2] region)

Smeekens SP, Avruch AS, LaMendola J, Chan SJ, Steiner DF. Identification of a cDNA encoding a second putative prohormone convertase related to PC2 in AtT20 cells and islets of Langerhans Proc Natl Acad Sci U S A 1991 Jan 15;88(2):340-4

Stijnen P, Ramos-Molina B, O'Rahilly S, Creemers JW. PCSK1 Mutations and Human Endocrinopathies: From Obesity to Gastrointestinal Disorders Endocr Rev 2016 Aug;37(4):347-71

Takumi I, Steiner DF, Sanno N, Teramoto A, Osamura RY. Localization of prohormone convertases 1/3 and 2 in the human pituitary gland and pituitary adenomas: analysis by immunohistochemistry, immunoelectron microscopy, and laser scanning microscopy Mod Pathol 1998 Mar;11(3):232-8

Tanaka S, Kurabuchi S, Mochida H, Kato T, Takahashi S, Watanabe T, Nakayama K. Immunocytochemical localization of prohormone convertases PC1/PC3 and PC2 in rat pancreatic islets Arch Histol Cytol 1996 Aug;59(3):261-71

Tzimas GN, Chevet E, Jenna S, Nguyên DT, Khatib AM, Marcus V, Zhang Y, Chrétien M, Seidah N, Metrakos P. Abnormal expression and processing of the proprotein convertases PC1 and PC2 in human colorectal liver metastases BMC Cancer 2005 Nov 17;5:149

Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, Olsson I, Edlund K, Lundberg E, Navani S, Szigyarto CA, Odeberg J, Djureinovic D, Takanen JO, Hober S, Alm T, Edqvist PH, Berling H, Tegel H, Mulder J, Rockberg J, Nilsson P, Schwenk JM, Hamsten M, von Feilitzen K, Forsberg M, Persson L, Johansson F, Zwahlen M, von Heijne G, Nielsen J, Pontén F. Proteomics Tissue-based map of the human proteome Science

Vindrola O, Mayer AM, Citera G, Spitzer JA, Espinoza LR. Prohormone convertases PC2 and PC3 in rat neutrophils and macrophages Parallel changes with proenkephalin-derived peptides induced by LPS in vivo Neuropeptides

Wilschanski M, Abbasi M, Blanco E, Lindberg I, Yourshaw M, Zangen D, Berger I, Shteyer E, Pappo O, Bar-Oz B, Martín MG, Elpeleg O. A novel familial mutation in the PCSK1 gene that alters the oxyanion hole residue of proprotein convertase 1/3 and impairs its enzymatic activity PLoS One 2014 Oct 1;9(10):e108878

Yourshaw M, Solorzano-Vargas RS, Pickett LA, Lindberg I, Wang J, Cortina G, Pawlikowska-Haddal A, Baron H, Venick RS, Nelson SF, Martín MG. Exome sequencing finds a novel PCSK1 mutation in a child with generalized malabsorptive diarrhea and diabetes insipidus J Pediatr Gastroenterol Nutr 2013 Dec;57(6):759-67

Zhang JH, Zhou D, You J, Tang BS, Li PY, Tang SS. Differential processing of neuropeptide proprotein in human breast adenocarcinoma J Endocrinol Invest 2013 Oct;36(9):745-52

Zhou A, Bloomquist BT, Mains RE. The prohormone convertases PC1 and PC2 mediate distinct endoproteolytic cleavages in a strict temporal order during proopiomelanocortin biosynthetic processing J Biol Chem 1993 Jan 25;268(3):1763-9

Zhou A, Martin S, Lipkind G, LaMendola J, Steiner DF. Regulatory roles of the P domain of the subtilisin-like prohormone convertases J Biol Chem 1998 May 1;273(18):11107-14

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