Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

PTHLH (parathyroid hormone-like hormone)

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Published in Atlas Database: July 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/PTHLHID41897ch12p11.html
DOI: 10.4267/2042/48490

This article is an update of :
Yeung SCJ. PTHLH (parathyroid hormone-like hormone). Atlas Genet Cytogenet Oncol Haematol 2008;12(3):234-239.

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Identity

Other names: HHM, osteostatin, PLP, PTHR, PTHRP
HGNC (Hugo): PTHLH
Location: 12p11.22

DNA/RNA

Description

PTHLH is encoded by a single gene that is highly conserved among species.
The gene is composed of 7 exons spanning a region of 13899 bases (start: 28002284 bp from pter; end: 28016183 bp from pter).
Orientation: minus strand.
The genomic DNA for the PTHLH gene was isolated from a human placental genomic library (Yasuda et al., 1989).

Transcription

The sequence is supported by 3 sequences from 3 cDNA clones.

Pseudogene

None.

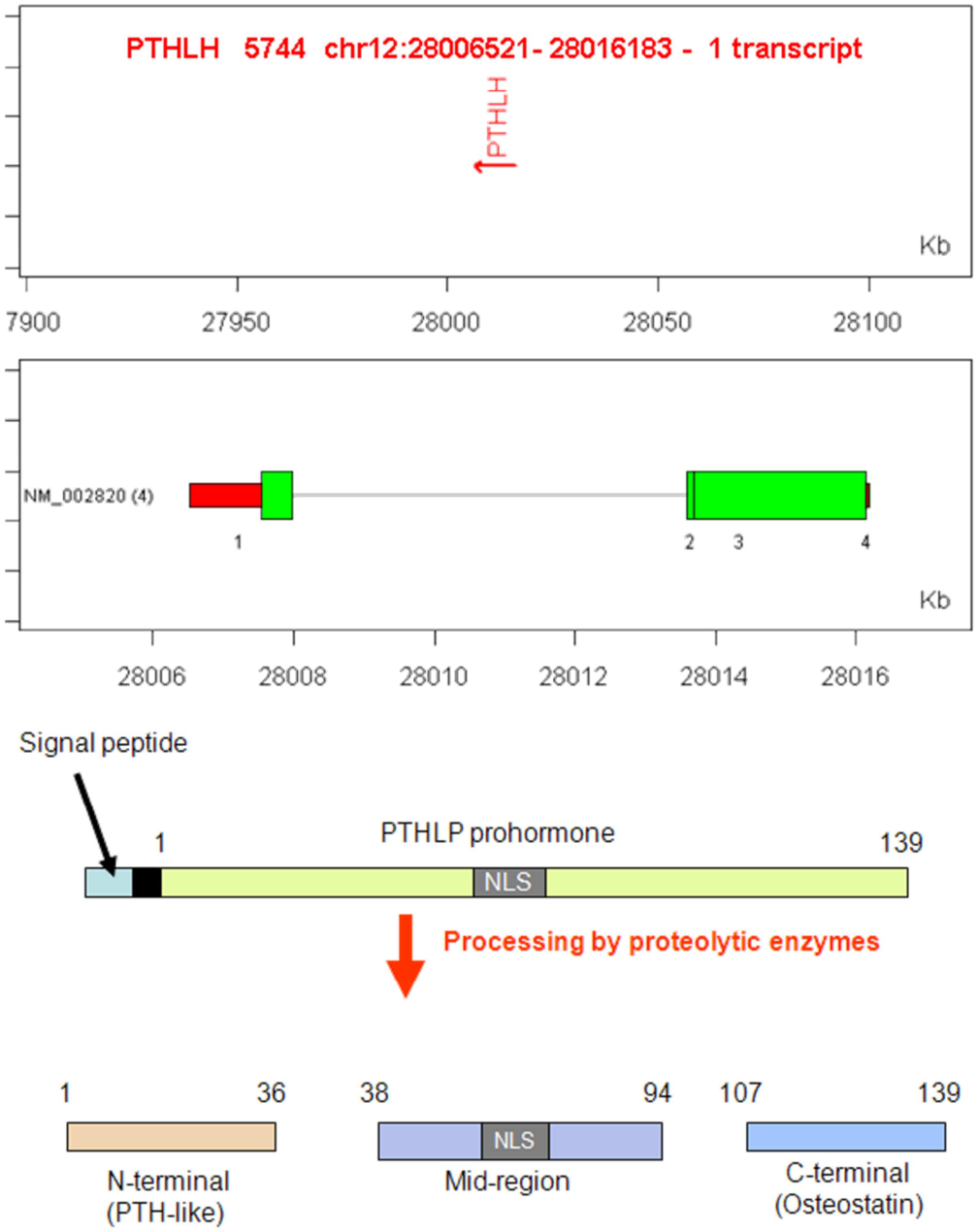
Protein

Description

Size: 177 amino acids, 20194 Da.
The PTHLH gene has seven exons, and its transcripts are processed by alternative splicing into three isoforms, encoding proteins with 139, 173 and 141 amino acid. The pattern of expression of PTHLH mRNA isoforms may be cell type-specific (Sellers et al., 2004). Although different tumors may have different PTHLH splicing patterns, there are no tumor-specific transcripts (Southby et al., 1995). PTHLH is processed into a set of distinct peptide hormones by endoproteolytic cleavage of the initial translation products: mature N-terminal, mid-region and C-terminal secretory peptides, each having its own distinct function. The distribution of the endopeptidase processing enzymes (PTP (prohormone thiol protease), prohormone convertases 1 and 2 (PC1 and PC2)) may vary in different tissues (Deftos et al., 2001). PTP cleaved the PTHLH precursor at the multibasic, dibasic, and monobasic residue cleavage sites to generate the NH2-terminal peptide (residues 1-37, having PTH-like and growth regulatory activities), the mid-region domain (residues 38-93, regulating calcium transport and cell proliferation), and the COOH-terminal domain (residues 102-141, modulating osteoclast activity) (Hook et al., 2001).

Expression

PTHLH is a protein polyhormone produced by most if not all tissues in the body. It is secreted during both fetal and postnatal life. Although PTHLH is found in the circulation, most of its activity appears to be paracrine.



This diagram represents schematically one possible proteolytic processing pattern of PTHLH into 3 bioactive peptides. The mid-region of PTHLH contains the nuclear localization signal (NLS).

A complex of transcription factors and coactivators (CREB, Ets1 and CBP) regulates PTHLH transcription and may contribute to the alterations associated with the promotion of carcinogenesis (Hamzaoui et al., 2007). Disruption of the normal regulation during cancer progression may in part be associated with TGF-beta1-induced changes in PTHLH mRNA isoform expression and stability (Sellers et al., 2004). TGF-β activates PTHLH expression increasing transcription from the P3 promoter through a synergistic interaction of Smad3 and Ets1 (Lindemann et al., 2001). ERK1/ERK2-dependent Ets2/PKCε synergism also appears to regulate PTHLH expression in breast cancer cells (Lindemann et al., 2003).

The PTHLH gene is also under the transcriptional control of glucocorticoids and vitamin D (Ikeda et al., 1989). 1,25-dihydroxy vitamin D3 treatment increases PTHLH mRNA expression and blocks the stimulatory effect of TGF-beta on PTHLH mRNA expression (Kunakornsawat et al., 2001). Glucocortical steroid hormone can suppress PTHLH mRNA expression and release of bioactive PTHLH in certain PTHLH-producing tumors (Kasono et al., 1991). The regulation of PTHLH expression by female sex steroid hormones is still unclear

(Kurebayashi and Soono, 1997; Sugimoto et al., 1999; Rabbani et al., 2005).
Glucocorticoids reduced PTHLH and PTH1R expression in human mesenchymal stem cells which could be one of the mechanisms involved in steroids induced bone loss (Ahlström et al., 2009).
In cell lines, upregulation of hypoxia induced factor HIF-2α subunit is involved in PTHLH upregulation (Manisterski et al., 2010).
PTHLH is a downstream target for RAS and SRC (Li and Drucker, 1994), K-ras mutation increases PTHLH expression (Kamai et al., 2001) while a farnesyltransferase inhibitor known to inhibit RAS function can decrease PTHLH expression (Dackiw et al., 2005). The von Hippel-Lindau tumor suppressor protein also negatively regulates PTHLH expression at the post-transcriptional level (Massfelder et al., 2004).

Localisation

PTHLH is a secreted polyhormone and is localized in the Golgi apparatus in the cytoplasm. However, in some cells, PTHLH can be detected in the nucleus by immunochemistry. The growth-inducing effect of NLS-containing mid-region PTHLH peptide in breast cancer is dependent on both internalization into the cytoplasm and subsequent translocation to the nucleus (Kumari et al., 2006). PTHLH travels from the cytosol to the nucleus with the help of the nuclear transport factor importin beta1. Importin beta1 enhanced the association of PTHLH with microtubules, and the microtubule cytoskeleton plays an important role in protein transport to the nucleus (Lam et al., 2002).
The site of recognition of PTHLH is the N-terminal half of importin, which can also bind Ran and nucleoporin, and is sufficient for PTHLH nuclear import (Conti, 2003).

Function

PTHLH is a growth factor, a PTH-like calciotropic hormone, a developmental regulatory molecule, and a muscle relaxant (Clemens et al., 2001). The diverse activities of PTHLH result not only from processing of the precursor into multiple hormones, but from use of multiple receptors.
It is clear that the Type 1 Parathyroid Hormone Receptor (PTH1R), binding both PTH (1-34) and PTHLH (1-36), is the receptor mediating the function of PTHLH (1-36), and it is the only cloned receptor for PTHLH so far (Clemens et al., 2001).
PTHLH also binds to a type of receptor in some tissues that does not bind PTH. PTHLH (67-86) activates phospholipase C signaling pathways through a receptor distinct from that activated by PTHLH (1-36) in the same cells (Orloff et al., 1996). Unlike PTH, picomolar concentrations of the PTHLH (107-111) fragment to can activate membrane-associated PKC in osteosarcoma cells (Gagnon et al., 1993). PTHLH (107-139) exerts effects through the PKC/ERK pathway (de Gortázar et al., 2006). Thus, it is highly likely that the mid-region and osteostatin peptides bind other, unique receptors, but those receptors have yet to be cloned and identified.
In contrast to the receptor-mediated endrocrine and paracrine action, the mid-region PTHLH peptide contains a classic bipartite nuclear localization signal (NLS) which upon entering the nuclear compartment confers "intracrine" actions. Details of the nuclear action of PTHLH are still lacking, but overall, nuclear PTHLH appears to be mitogenic (de Miguel et al., 2001). The translation of PTHLH initiates from both the methionine-coding AUG and a leucine-coding CUGs further downstream in its signal sequence. It appeared that when translation was initiated from CUGs, PTHLH accumulated in the nucleoli, and that when translation was initiated from AUG, PTHLH localized in both the Golgi apparatus and nucleoli. Thus, nucleolar PTHLH appears to be derived from translation initiating from both AUG and CUGs (Amizuka et al., 2002). Modulation of cell adhesion by PTHLH localized in the nucleus is a normal physiological action of PTHLH, mediated by increasing integrin gene transcription (Anderson et al., 2007). The promotion by PTHLH in cancer growth and metastasis may be mediated by upregulating integrin alpha6beta4 expression and activating Akt (Shen and Falzon, 2006).
PTHLH also interacts with beta-arrestin 1B, an important component of MAPK signaling and G-protein-coupled receptor desensitization, and this interaction requires residues 122-141 of PTHLH. Therefore, beta-arrestin 1 may mediate a novel regulatory function of PTHLH in intracellular signaling (Conlan et al., 2002).
PTHLH also play a major role in development of several tissues and organs.
PTHLH stimulates the proliferation of chondrocytes and suppresses their terminal differentiation. PTHLH (107-139) is a substrate for secPHEX, and osteocalcin, pyrophosphate and phosphate are inhibitors of secPHEX activity; thus PHEX activity and PTHLH are part of a complex network regulating bone mineralization (Boileau et al., 2001). PTHLH plays a central role in the physiological regulation of bone formation, by promoting recruitment and survival of osteoblasts, and probably plays a role in the physiological regulation of bone resorption, by enhancing osteoclast formation.
Signaling by fibroblast growth factor receptor 3 and PTHLH coordinate in cartilage and bone development (Amizuka et al., 2004). PTHLH is also an essential physiological regulator of adult bone mass (Bisello et al., 2004).
In oophorectomized mice, injecting PTHLH fragments increased bone formation and reduced bone resorption (de Castro et al., 2012).

Subcutaneous PTHLH injections in healthy postmenopausal women resulted in a pure anabolic effect on bone and increase intestinal calcium absorption when given in high doses (Horwitz et al., 2010).
PTHLH maintains chondrocytes and growth plates as the inhibition of PTHLH signaling via PTH/PTHLH receptor in chondrocytes resulted in an accelerated differentiation of chondrocytes and premature disappearance of the growth plates (Hirai et al., 2011). PTHLH signaling stimulates chrondrocytes proliferation. This process is inhibited via WNT/beta catenin signaling that in turn stimulates chondrocytes hypertrophy (Guo et al., 2009).
In giant cell tumors, stromal cell production of PTHLH increased RANK ligand expression and led to giant cell formation (Cowan et al., 2012).
PTHLH increased the survival of giant cell tumor stromal cells in vitro while the neutralization of PTHLH signaling induced cell death through the activation of different pathways (caspase, TRAIL, JAK-STAT, and cyclin E/CDK2) (Mak et al., 2012).
PTHLH aids in normal mammary gland development and lactation as well as placental transfer of calcium. Mammary gland development depends upon a complex interaction between epithelial and mesenchymal cells that requires PTHLH. The calcium sensor (CaR) regulates PTHLH production as well as transport of calcium in the lactating mammary gland (Ardeshirpour et al., 2006). In normal animals, mammary epithelial cells secrete a lot of PTHLH, which helps to adjust maternal metabolism to meet the calcium demands of lactation. The mid-region PTHLH peptide has also been shown to control the normal maternal-to-fetal pumping of calcium across the placenta.
Rarely, placental PTHLH production can lead to pregnancy associated hypercalcemia. Hypercalcemia in pregnancy could have significant morbidity but tend to resolve post-delivery (Eller-Vainicher et al., 2012).
PTHLH is secreted from smooth muscle in many organs, usually in response to stretching. PTHLH relaxes smooth muscle. Transgenic mice that express PTHLH in vascular smooth muscle have hypotension, being consistent with a vasodilating effect of PTHLH.
PTHLH is highly expressed in the skin. EGF and other similar ligands can potentially activate PTHLH gene expression in the epidermis (Cho et al., 2004). PTHLH can inhibit hair growth and is required for tooth eruption as shown by mouse models that manipulated the PTHLH gene.
In rodent and human pancreatic beta cell cultures, PTHLH (1-36) enhanced the proliferation and function of beta cells. Injecting male mice with PTHLH (1-36) increased beta cell proliferation via increased levels of cyclin D2 and decreased levels of Ink4a (Williams et al., 2011).
PTHLH activates BMP-2/ Cbfa1 signaling pathway which could lead to vascular calcifications in hemodialysis patients (Liu et al., 2012).
In addition, PTHLH overexpression increased arterial vascular smooth muscle cells proliferation resulting in arterial stenosis (Sicari et al., 2012).

Implicated in

Humoral hypercalcemia of malignancy

Prognosis

The median survival after the first occurrence of hypercalcemia is 66 days in patients with serum PTHLH $\leq$ 21 pmol/L and 33 days in patients with PTHLH > 21 pmol/L. In hypercalcemia of malignancy, raised serum levels of PTHLH indicate a more advanced tumor state and an extremely poor prognosis (Pecherstorfer et al., 1994).

Oncogenesis

Humoral hypercalcemia of malignancy (HHM) was first described by Albright in 1941 (Albright, 1941), and is a well-known complication among cancer patients. This syndrome is commonly encountered in advanced cancer of epithelial origin, especially squamous cell carcinoma of the lung. Studies of the "humors" secreted by cancer that causes hypercalcemia led to the discovery of 3 classes of peptides: parathyroid-like peptides, growth factor-like peptides, and bone-resorbing factors. Then protein purification led to molecular studies that cloned cDNAs for PTHLH (Suva et al., 1987; Broadus et al., 1988; Mangin et al., 1988). Suva et al. (Suva et al., 1987) suggested that the PTHLH may be responsible for the abnormal calcium metabolism in HHM.
In the mammary epithelium of breast cancer mouse model, PTHLH inhibition delayed tumor formation and spread with reduction of markers of angiogenesis and cell proliferation (Li et al., 2011).
PTHLH can be expressed in many tumors and leads to chemotherapy resistance as it inhibits apoptosis via downregulation of proapoptotic factors including Bax, and PUMA while upregulating antiapoptotic factors (Bcl-2, and Bcl-xl) (Gagiannis et al., 2009).

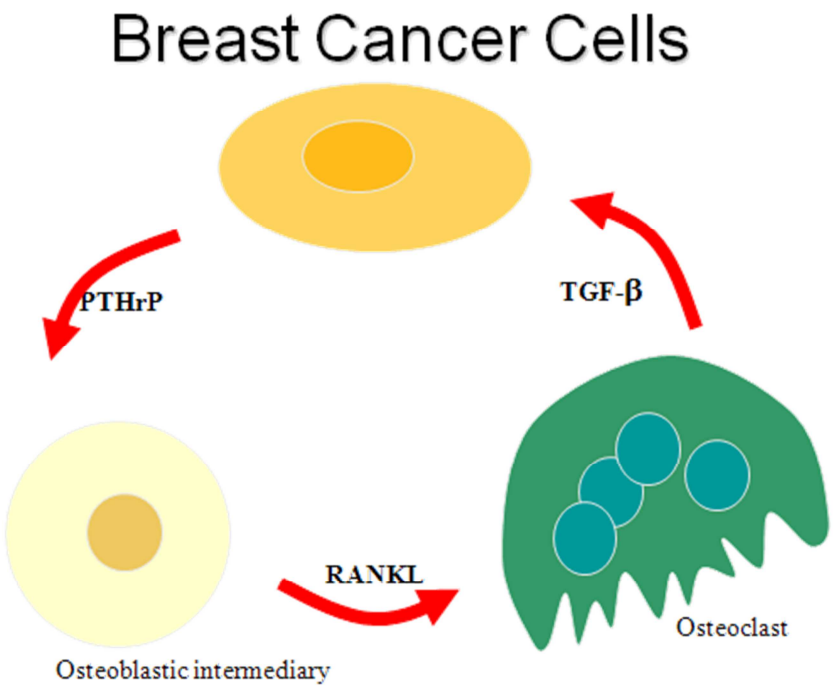
Autocrine promotion of tumor progression

Prognosis

In the absence of hypercalcemia, approximately 17% of patients with gastroesophageal carcinoma have elevated levels of PTHLH, and the increase in PTHLH was associated with a poor prognosis (Deans et al., 2005).

Oncogenesis

mRNA for the PTH1R was detected many tumors expressing PTHLH; thus the PTHLH produced by these tumors may act in an autocrine or paracrine fashion (Southby et al., 1995; Alokail and Peddie, 2007; Gessi et al., 2007).



The interactions among breast cancer cells, osteoblasts and osteoclasts define a feedback loop that promote breast cancer growth in the bone microenvironment.

PTHLH (1-34) treatment resulted in an increase in proliferation in prostate cancer cells which may require androgen in some cell lines (Asadi et al., 2001). In breast cancer cells, PTHLH regulates CDC2 and CDC25B via PTH1R in a cAMP-independent manner, and PTHLH promotes cell migration through induction of ITGA6, PAI-1, and KISS-1, and promotes proliferation through induction of KISS-1 (Dittmer et al., 2006). These pieces of evidence together suggest that PTHLH and PTH1R together play an important role in the autocrine/paracrine promotion of tumor proliferation in some cancers.

Bone metastasis

Disease

Breast cancer

Oncogenesis

PTHLH is a mediator of the bone destruction associated with osteolytic metastasis. Patients with PTHLH-expressing breast carcinoma are more likely to develop bone metastasis, and bone metastasis expresses PTHLH in >90% of cases as compared with <20% of cases of metastasis to other sites (Powell et al., 1991).

In breast cancer, osteolytic metastases are the most common. PTHLH is a common osteolytic factor, and other osteolytic factors include vascular endothelial growth factor and interleukin 8 and interleukin 11. Since osteoblasts are the main regulators of osteolytic osteoclasts, stimulation of osteoblasts can paradoxically increase osteoclast function. Simultaneous expression of osteoblastic and osteolytic factors can produce mixed metastases.

PTHLH expression by cancer cells may provide a selective growth advantage in bone because PTHLH stimulates osteoclastic bone resorption to release growth factors such as TGF-beta from the bone matrix. TGF-beta in turn will activate by osteoclastic bone resorption and enhance PTHLH expression and tumor cell growth (Yin et al., 1999), thus completing a vicious cycle (see diagram). Taken together, PTHLH expression by breast carcinoma cells enhance the development and progression of breast carcinoma metastasis to bone (Guise et al., 1996). Alternatively, cytokines such as IL-8 initiate the process of osteoclastic bone resorption in the early stages of breast cancer metastasis, and PTHLH expression is induced to stimulate the vicious cycle of osteolysis at a later stage (Bendre et al., 2003).

Certain cancer treatments, especially sex steroid hormone deprivation therapies, stimulate bone loss. Bone resorption will result in the release of bone growth factors, which may inadvertently facilitate bone metastasis (Guise, 2000). Treatment with bisphosphonates will prevent bone resorption and reduce the release of bone growth factors (Guise et al., 2005).

Cachexia in hypercalcemia of malignancy

Oncogenesis

PTHLH induces a wasting/cachectic syndrome (Iguchi et al., 2001). PTHLH leads to decreased physical activity and lowered energy metabolism independently of the effects of hypercalcemia and

proinflammatory cytokines (Onuma et al., 2005). In a rodent model, PTHLH induces a cachectic syndrome (in addition to inducing hypercalcemia of malignancy) by changing the mRNA levels of orexigenic and anorexigenic peptides, except leptin and orexin (Hashimoto et al., 2007). Expression of cachexia-inducing cytokines such as interleukin-6 and leukemia inhibitory factor is increased by PTHLH (Iguchi et al., 2006). Animal data suggest that humanized antibody against PTHLH may be effective for patients with hypercalcemia and cachexia in patients with humoral hypercalcemia of malignancy (Sato et al., 2003).

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This article should be referenced as such:

Yeung SCJ, Habra MA. PTHLH (parathyroid hormone-like hormone). Atlas Genet Cytogenet Oncol Haematol. 2013; 17(2):94-101.