KLK5 (Kallikrein-related peptidase 5)

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Identity

Other names: EC 3.4.21; HSCTE; KLK-L2; KLKL2; SCTE
HGNC (Hugo): KLK5
Location: 19q13.41
Local order: Telomere to centromere.

DNA/RNA

Description
The KLK5 gene is approximately 9.5 kb in length, consisting of 6 exons (5 of them are coding exons) and 5 introns.

Transcription
Five alternatively spliced variants have been identified for the KLK5 gene. These variants differ in the number and length of the 5’ untranslated exons and/or the last two coding exons. Tissue-specific expression of these variants is regulated by multiple promoters located in the first exon of each isoform. KLK5 splice variants were found to be differentially expressed, at the mRNA level, in ovarian, breast and prostate cancers.

Pseudogene
None identified.

Protein

Description
Full-length KLK5 is formed of 293 amino acids. It is composed of a signal peptide (29 amino acids), followed by an activation peptide (37 amino acids) and the mature chain (227 amino acids), with 4 potential N-linked glycosylation sites. The position of the catalytic triad of serine proteases is conserved. KLK5 is synthesized as a full-length protein intracellularly. In the secretory pathway, the signal peptide is cleaved and the zymogen is released outside the cells. Upon activation, the propeptide is removed to generate the mature active protein. In serum and ascites fluid, in addition to the free (approximately 40 kDa) form, KLK5 forms complexes with alpha(1)-antitrypsin and alpha(2)-macroglobulin.

Expression
At the mRNA level, KLK5 is expressed in a variety of tissues, mainly the testis, brain, breast, thyroid and salivary glands. The KLK5 protein is expressed at higher levels in the skin, salivary gland, testis and female genital organs. KLK5 has also been identified in many biological fluids, including vaginal secretions, breast milk and seminal plasma. Many fetal tissues, including bone, skin, thymus and kidney also express KLK5.

Localisation
KLK5 is a secreted protein.

Function
KLK5 is a secreted serine protease. The physiological functions of KLK5 are not fully understood. The KLK5 protein was originally identified from a keratinocyte library and was purified from the stratum corneum of the human skin. It was found to have a trypsin-like enzymatic activity with strong preference for Arg over Lys in the P1 position. Evidence exists that it plays a role in skin desquamation. KLK5 can also digest extracellular matrix components, collagens type I, II, III, IV, fibronectin, and laminin, and can potentially release angiostatin from plasminogen, and "cystatin-like domain 3" from low molecular weight kininogen, and fibrinopeptide B and peptide beta15-42 from the BGL2.
beta chain of fibrinogen. The KLK5 protein has been shown to activate another kallikrein, KLK7, and was found to be under steroid hormonal regulation in cancer cell lines. It has been recently shown that KLK5 is differentially expressed in a number of malignancies, including ovarian, breast and prostate cancers, but the mechanisms of its involvement in cancer have yet to be determined.

**Homology**

The human KLK5 protein sequence shares 40-70% homology with other members of the human tissue kallikreins, and 70% identity with that of the mouse orthologue.

**Mutations**

*Note*

No germinal or somatic mutations are identified to be associated with cancer so far.

**Implicated in**

**Ovarian cancer**

*Disease*

Higher KLK5 concentrations were found in the serum of 69% of patients with ovarian cancer. The KLK5 protein was found to be elevated in 55% of ovarian cancer tissues compared to normal. Also, KLK5 mRNA is significantly elevated in ovarian cancer, especially serous type. Ovarian cancer ascites contains higher levels, as compared to benign effusions and ascites from other cancer types. Two KLK5 splice variants are upregulated in ovarian cancer tissues compared to normal.

*Prognosis*

The KLK5 mRNA and protein are markers of unfavorable prognosis in ovarian cancer, being overexpressed in late stage and higher grade tumors, and associated with shorter DFS and OS. In addition, the KLK5 protein was shown to be an independent indicator of poor prognosis in patients with high-grade tumors and optimal debulking success.

*Cytogenetics*

No cytogenetic abnormalities are identified so far.

*Hybrid/Mutated gene*

None identified.

**Breast cancer**

*Disease*

Higher concentrations of KLK5 were found in the serum of 49% of patients with breast cancer. KLK5 splice variant 2 is downregulated in breast cancer compared to normal.

*Prognosis*

The KLK5 mRNA transcript was found to be an indicator of unfavorable prognosis, being overexpressed in node-positive patients with ER-negative tumors. It is independently associated with decreased DFS and OS, and it is an independent indicator of shorter DFS and OS in node-positive patients.

*Cytogenetics*

No cytogenetic abnormalities are identified so far.

*Hybrid/Mutated gene*

None identified.

**Prostate cancer**

*Disease*

KLK5 mRNA is downregulated in cancer vs normal prostatic tissues.

*Prognosis*

KLK5 mRNA is a favorable prognostic marker, with higher levels associated with low grade tumors and low Gleason score.

*Cytogenetics*

No cytogenetic abnormalities are identified so far.

*Hybrid/Mutated gene*

None identified.

**Testicular cancer**

*Disease*

KLK5 mRNA is downregulated in cancer vs normal testicular tissues.

*Prognosis*

KLK5 mRNA is a marker of favorable prognosis, overexpressed in smaller, early stage non-seminomas.

*Cytogenetics*

No cytogenetic abnormalities are identified so far.

*Hybrid/Mutated gene*

None identified.

**Non-small cell lung carcinoma**

*Disease*

Serum KLK5 levels are lower in lung cancer compared to normal and can be used as part of a multiparametric panel for diagnosis.

*Prognosis*

None identified.

*Cytogenetics*

No cytogenetic abnormalities are identified so far.

*Hybrid/Mutated gene*

None identified.

**Urinary bladder carcinoma**

*Disease*

None identified.

*Prognosis*

Increased expression of KLK5 was frequently observed in invasive tumors (pT2-pT4) compared with superficial tumors (pTa, pT1).
Cytogenetics
Copy number gain was observed in transitional cell carcinoma.

Hybrid/Mutated gene
None identified.

Breakpoints
Note
None identified.

References


This article should be referenced as such: