KLK11 (Kallikrein-related peptidase 11)

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Identity

Other names: Hippostasin; hK11; PRSS20; TLSP
HGNC (Hugo): KLK11
Location: 19q13.41
Local order: Telomere to centromere.

DNA/RNA

Description

The KLK11 gene is about 5.8 Kb in length, consisting of 6 exons and 5 introns.

Transcription

Three alternatively spliced variants have been described in the literature: including isoform 1, isoform 2, and isoform 3. Isoform 1 is preferentially expressed in the brain and it encodes a protein of 250 amino acids. Isoform 2 and isoform 3 are mainly expressed in the prostate. Compared to isoform 1, isoform 2 has additional 32 amino acids at the N-terminus and isoform 3 contains extra 25 amino acids inserted in the catalytic triad. Tissue-specific expression of these isoforms is regulated by multiple promoters that locate in the first exon of each isoform.

Pseudogene

Not identified so far

Protein

Description

Full-length KLK11 is composed of a signal peptide (aa 1-50), a propeptide (aa 51-53), and a mature chain (aa 54-282). KLK11 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.

Expression

KLK11 is mainly expressed in epithelial tissues, such as stomach, trachea, and skin, with high levels in the brain and the prostate. KLK11 has also been identified in many biological fluids. Seminal plasma, containing an average of 15 µg/mL of KLK11, is the biological fluid reported to have the most abundant KLK11 so far. Other specimens, including serum, lactating milk, cerebrospinal fluid, and amniotic fluid, all have detectable amounts of KLK11.

Localisation

Secreted.

Function

The physiology functions of KLK11 and the mechanisms of its involvement in cancer have yet to be determined. Using positional scanning combinatorial tetrapeptide substrate library, it has revealed that KLK11 preferentially cleaves peptide bonds after methionine, arginine, and lysine. However, its physiology substrates remain unidentified. One hypothesis is that KLK11 may be part of a proteolytic cascade consisting of multiple kalli-kreins (KLKs). Since KLK11 is unable to auto-activate, in the cascade, it is likely that KLK11 is activated by upstream KLKs, then subsequently activate/inactivate other downstream KLKs or other proteins. Accumulating experimental evidence is in accord with this hypothesis. It has been shown in vitro experiments that, both KLK12 and KLK14 are able to activate KLK11. Another hypothesis is that KLK11 may be involved in the homeostasis of insulin growth factor. This hypothesis comes from the observation that KLK11 is able to degrade insulin growth factor binding...
protein 3 (IGFBP3) to facilitate the release of insulin growth factor. KLK11 enzymatic activity is mainly regulated by internal cleavage. In seminal plasma, about half the KLK11 is in the cleaved inactive form. Some abundant serine protease inhibitors present in the circulation or in seminal plasma, such as α1-antitrypsin, protein C inhibitor, α2-antiplasmin, and C1 inhibitor, fail to show rapid inhibition of KLK11.

**Homology**

Human KLK11 protein sequence shares 98% and 82% identity with that of chimpanzee and dog/bovine/mouse/rat, respectively.

**Mutations**

**Note**

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

**Implicated in**

**Prostate cancer**

**Disease**

A number of investigations have been reported concerning the role of KLK11 as a potential diagnostic biomarker for prostate cancer (CaP). Prostate specific antigen (PSA) is currently the most widely used diagnostic marker for CaP. However, measuring PSA alone is lack of specificity, since some benign prostatic diseases, such as benign prostatic hyperplasia (BPH) and prostatitis, can also have increased serum PSA levels, whereas some CaP patients may have only mild elevation of PSA (4-10 ng/mL). To improve the specificity, a number of additional analyses, such as measuring the molecular forms of PSA, have been proposed. Patients with low free to total PSA ratios are considered to have higher risk of developing CaP. In spite of these efforts, false positive and false negative still occur and doctors frequently need to rely on prostate biopsy to make the final diagnosis. Some investigations have shown that measuring serum KLK11 concentrations may help discriminate CaP from BPH and reduce the number of unnecessary biopsies. Similar to PSA, serum KLK11 concentrations are elevated in the majority of CaP patients. However, compared to the BPH patients, the CaP patients tend to have lower serum KLK11 concentrations and lower KLK11 to total PSA ratios. In those patients that have less than 20% free PSA, measuring KLK11 to total PSA ratio identified 54% to have BPH. As such, it seems that KLK11 to total PSA ratio might be a complementary marker for free PSA percentage and combination of these two markers results in better specificity for CaP. KLK11 might not be superior to PSA in population screening. In a retrospective study, serum KLK11 or KLK11 to PSA ratio showed no advantage over PSA alone to differentiate CaP patients from noncancer individuals whose total PSA levels are in the range of 2.5 to 10 ng/mL.

**Prognosis**

Tissue expression levels of KLK11 may be used as a prognostic indicator for prostate cancer. Lower KLK11 mRNA levels have been found to be associated with higher tumor grade, tumor stage, and Gleason score, suggesting that KLK11 might be able to indicate the aggressiveness of prostate tumors.

**Cytogenetics**

No cytogenetic abnormalities are identified so far.

**Hybrid/Mutated gene**

Not identified so far.

**Ovarian cancer**

**Disease**

KLK11 has shown promise as a diagnostic biomarker for ovarian cancer. Earlier studies have revealed that serum KLK11 concentrations are elevated in the majority of ovarian cancer patients. Subsequent investigations further demonstrate that KLK11 is able to distinguish ovarian cancer cases from healthy controls. More importantly, it is less sensitive to benign ovarian diseases than is CA125, the most widely used diagnostic marker for ovarian cancer. Moreover, it has high temporal stability, which implies that it could be used in a longitudinal screening program for early detection.

**Prognosis**

Many investigations have clearly demonstrated that KLK11 has elevated protein levels in primary ovarian tumors than in normal tissue, benign or nonovarian metastatic tumors. In general, higher levels of KLK11 in ovarian tumor extracts are predictive of favorable outcome. They are more likely to be associated with early stage, responsive to chemotherapy, and longer progression free survival.

**Cytogenetics**

No cytogenetic abnormalities are identified so far.

**Hybrid/Mutated gene**

Not identified so far.

**Lung cancer**

**Prognosis**

The prognostic role of KLK11 has also been explored in lung cancer both at the mRNA and protein levels. With quantitative PCR, it has shown that KLK11 mRNA levels are lower in tumor tissues in comparison with adjacent normal counter-parts. No significant correlation is identified with clinical stages, tumor status, and lymph node status. However, those patients with low KLK11 mRNA expression seem to have a significantly worse prognosis than those with high levels. At the protein level, serum KLK11 concentrations in non-small cell lung cancer patients are higher than in healthy controls and they are positively correlated with tumor stages.
Cytogenetics
No cytogenetic abnormalities are identified so far.

Hybrid/Mutated gene
Not identified so far.

Breakpoints
Note
Not described so far.

References


This article should be referenced as such: