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KLK15 AS A NEW PROGNOSTIC BIOMARKER IN PROSTATE CANCER

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ABSTRACT

Prostate cancer is one of the most frequently diagnosed malignancies among men worldwide and remains a major public health challenge. Despite significant advances in diagnostic methods, commonly used biomarkers such as prostate-specific antigen (PSA) have important limitations, including relatively low specificity and the risk of overdiagnosis. Consequently, considerable research efforts have focused on identifying novel molecular biomarkers that could improve diagnostic accuracy and provide additional prognostic information in patients with prostate cancer.

Among potential candidates, members of the human tissue kallikrein family (KLKs) have attracted particular attention. These serine proteases are involved in various biological processes, including extracellular matrix remodeling, regulation of the tumor microenvironment, and modulation of cellular signaling pathways. Dysregulation of kallikrein expression has been reported in multiple types of cancer, including prostate cancer.

Kallikrein-related peptidase 15 (KLK15) is one of the members of this family that has recently been investigated in the context of prostate cancer biology. Molecular studies have demonstrated increased KLK15 expression in prostate cancer tissues compared with normal prostate tissue. Furthermore, several studies have indicated associations between KLK15 expression levels and clinicopathological parameters, including tumor stage, Gleason score, and progression of free survival. These findings suggest that KLK15 may represent a promising prognostic biomarker in prostate cancer.

This review summarizes current knowledge regarding the structure and biological function of KLK15, its expression patterns in prostate cancer, and its potential prognostic significance. Although available data indicate that KLK15 may have clinical relevance as a molecular biomarker, further studies involving larger patient cohorts are required to fully establish its diagnostic and prognostic value.

KEYWORDS

Prostate Cancer, KLK15, Kallikrein Related Peptidases, Biomarkers, Gene Expression, Prognosis, Molecular Diagnostics

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Introduction

Prostate cancer is one of the most common malignant neoplasms among men and represents a significant public health problem worldwide. The disease occurs predominantly in middle-aged and older individuals, and its incidence increases with age. According to epidemiological data, more than 1.4 million new cases of prostate cancer and approximately 375,000 deaths were reported in 2020, making it the second most frequently diagnosed cancer in the male population globally [1,2].

The diagnosis of prostate cancer is primarily based on the histopathological evaluation of prostate tissue obtained by biopsy. In clinical practice, the diagnostic process typically involves digital rectal examination (DRE), measurement of serum prostate specific antigen (PSA) levels, and imaging techniques, particularly multiparametric magnetic resonance imaging (mpMRI), which has significantly improved the detection of clinically significant prostate cancer [3].

Despite its widespread use in clinical practice, PSA testing has important limitations, including relatively low specificity, as elevated PSA levels may also occur in benign prostate conditions such as benign prostatic hyperplasia or prostatitis. In the Prostate Cancer Prevention Trial, prostate cancer was detected in approximately 26.9% of men with PSA levels between 3.1 and 4.0 ng/ml who underwent prostate biopsy. Consequently, PSA-based screening may lead to unnecessary biopsies as well as the overdiagnosis of clinically insignificant tumors [4,5].

Therefore, considerable research efforts have been directed toward the identification of novel molecular biomarkers that could improve diagnostic accuracy and enable a more precise assessment of prognosis in patients with prostate cancer. In recent years, particular attention has been focused on the family of human tissue kallikreins (KLKs), which comprises 15 genes encoding serine proteases. These genes play important

roles in numerous biological processes, including regulation of the tumor microenvironment, extracellular matrix remodeling, and inflammatory responses. Dysregulation of kallikrein expression has been observed in various types of cancer, and several members of this family have been proposed as potential diagnostic and prognostic biomarkers in malignancies, including prostate cancer [6].

One member of this family is kallikrein-related peptidase 15 (KLK15), whose expression has been reported to be increased in prostate cancer tissues compared with normal prostate tissue, suggesting a potential role of KLK15 in the pathogenesis and progression of prostate cancer. [7].

The kallikrein family (KLKs) and their role in cancer

The family of human tissue kallikreins (KLKs) represents the largest cluster of genes encoding serine proteases in the human genome and is located within a gene cluster on chromosome 19q13.4. Genes belonging to this family exhibit considerable sequence of similarity and a comparable structural organization, suggesting a common evolutionary origin. The products of these genes are synthesized as inactive preproenzymes that undergo proteolytic activation to form enzymatically active proteases. The proteolytic activity of kallikreins enables the degradation of various protein substrates and modulation of cellular signaling pathways, which may influence processes involved in tumor development and progression [6].

The expression of KLK family genes is regulated by various transcription factors and hormonal mechanisms. In particular, androgen dependent regulation plays an important role in the physiology of the prostate gland and in the development of prostate-related diseases. Kallikreins exhibit diverse expression patterns in many tissues and can be detected in various biological fluids, including blood, breast milk, and seminal plasma. This characteristic increases their potential usefulness as diagnostic biomarkers in cancer related diseases [6,8].

The best known member of this family is prostate specific antigen (PSA), also known as KLK3, which is one of the most widely used biomarkers in the diagnosis of prostate cancer [6].

Characteristics of the KLK15 gene

The KLK15 gene belongs to the family of human tissue kallikreins and is located within the kallikrein gene cluster on chromosome 19q13.4, between the KLK1 and KLK3 genes. The gene structure consists of five coding exons and four introns. KLK15 has been shown to be expressed at the mRNA level in various human tissues, with relatively high expression observed in steroid hormone dependent tissues, including the prostate [7].

Molecular analyses have revealed the presence of several KLK15 transcript variants generated through alternative RNA splicing. This mechanism may lead to the production of different protein isoforms and indicates complex regulation of gene expression. More recent studies have identified additional KLK15 transcript variants, further confirming the considerable transcriptional complexity of this gene and suggesting its potential biological relevance in both normal and malignant tissues [9].

Expression of KLK15 in prostate cancer

Molecular studies have shown that the expression of the KLK15 gene is increased in prostate cancer tissues compared with normal prostate tissue. Analysis of KLK15 mRNA expression in prostate samples demonstrated significantly higher levels of this gene in tumor tissues, suggesting that KLK15 may be involved in processes related to tumor transformation and the progression of prostate cancer [7]. Further studies investigating KLK15 transcript variants revealed significant differences in gene expression between prostate cancer and benign prostatic hyperplasia (BPH). Logistic regression analysis demonstrated that the expression level of the classical KLK15 transcript was significantly higher in patients with prostate cancer compared with patients with BPH (OR = 1.79; 95% CI: 1.34–2.39; $p < 0.001$). In multivariate analysis, KLK15 expression also showed significant value in distinguishing prostate cancer from benign prostatic conditions (OR = 1.96; 95% CI: 1.31–2.95; $p = 0.001$) [8].

Analysis of KLK15 expression in paired samples of normal and cancerous prostate tissue demonstrated increased gene expression in the majority of prostate cancer cases. In a study involving 25 patients, elevated KLK15 expression in tumor tissue was observed in 17 cases, whereas decreased expression was found in 8 cases. Overall, KLK15 expression was significantly higher in cancerous tissue compared with normal prostate tissue ($p = 0.045$). Moreover, increased KLK15 expression was associated with higher Gleason scores and more advanced tumor stage, suggesting a potential relationship between KLK15 expression and prostate cancer aggressiveness [11].

Clinical studies have also indicated the potential prognostic significance of KLK15. Increased expression of this gene was associated with shorter **progression free survival** in patients undergoing radical prostatectomy, suggesting that KLK15 may represent a promising prognostic biomarker in prostate cancer. [10].

Table 1. Selected studies investigating KLK15 in prostate cancer

Study	Year	Study design / Material	Key findings	Statistical data
Yousef et al.	2001	Prostate tissue samples; mRNA analysis	Increased KLK15 expression in prostate cancer tissue	$p < 0.05$
Mavridis et al.	2010	PCa vs BPH tissue samples; transcript analysis	Higher KLK15 transcript expression in PCa	OR = 1.79; 95% CI: 1.34–2.39; $p < 0.001$
Rabien et al.	2010	25 paired PCa and normal prostate samples	Increased KLK15 expression in tumor tissue	17 vs 8 cases; $p = 0.045$
Adamopoulos et al.	2020	Transcriptome analysis	6 novel KLK15 transcript variants identified	—

Abbreviations: PCa – prostate cancer; BPH – benign prostatic hyperplasia; OR – odds ratio; CI – confidence interval

Prognostic significance of KLK15 in prostate cancer

The prognostic significance of the KLK15 gene in prostate cancer has been primarily investigated through studies evaluating its mRNA expression levels in tumor tissues. Quantitative analyses demonstrated that the expression of the classical KLK15 transcript is significantly higher in prostate cancer samples compared with benign prostate tissue ($p < 0.001$). Moreover, elevated KLK15 expression was associated with more advanced pathological tumor stage ($p = 0.023$) as well as shorter progression-free survival determined by biochemical recurrence ($p = 0.006$). In multivariate Cox regression analysis, KLK15 expression was also identified as an independent predictor of prostate cancer recurrence (HR = 3.36; $p = 0.038$), suggesting that this gene may have potential utility as a prognostic biomarker in patients undergoing radical prostatectomy [12].

Additional studies also suggest a relationship between KLK15 expression and the biological aggressiveness of prostate cancer. Analyses of tissue samples obtained during radical prostatectomy demonstrated differences in KLK15 mRNA expression between malignant and histologically normal prostate tissue. Some studies have also reported associations between the expression of kallikrein family genes and clinicopathological features of prostate cancer, including tumor stage and Gleason score. These findings indicate that alterations in KLK15 expression may be related to the clinical course of prostate cancer and may provide additional information for prognostic assessment in affected patients [13].

An important aspect of KLK15 research is the analysis of transcript variants generated through alternative RNA splicing. The KLK15 gene exhibits considerable transcriptional complexity, and individual transcript variants may show different expression patterns in malignant and benign prostate tissues. In one study, a KLK15 transcript variant with intron III retention was identified and detected in 8 of 12 analyzed prostate cancer samples. These findings suggest that the evaluation of specific KLK15 transcript variants may provide additional insight into molecular mechanisms involved in prostate cancer development and may further improve the diagnostic and prognostic value of this gene [14].

In addition to differences in expression levels observed in tumor tissues, kallikreins have also been suggested to play a direct role in biological processes associated with cancer development and progression. Proteases belonging to this family participate in the degradation of extracellular matrix components and in the regulation of cellular signaling pathways that influence tumor cell proliferation, migration, and invasion, thereby facilitating tumor invasion and progression [15].

The role of kallikrein genes in prostate cancer has also been investigated in the context of their potential use as prognostic biomarkers. Several members of the kallikrein family have been shown to provide information related to disease progression and the risk of tumor recurrence. Consequently, molecular biomarkers are increasingly considered as complementary tools to classical clinical parameters used in prostate cancer prognosis, such as PSA level, tumor stage, and Gleason score. In this context, KLK15 has been investigated as a potential molecular marker that may provide additional prognostic information in patients with prostate cancer [16].

In summary, current evidence suggests that KLK15 may represent a potential prognostic biomarker in prostate cancer; however, its clinical relevance requires further investigation in larger patient cohorts and studies integrating molecular findings with clinical parameters [17].

Conclusions

Prostate cancer remains one of the most prevalent malignancies affecting men worldwide, highlighting the need for improved diagnostic and prognostic biomarkers. Although prostate-specific antigen (PSA) remains the most widely used biomarker in clinical practice, its limited specificity has stimulated extensive research into alternative molecular markers.

Among these candidates, kallikrein-related peptidase 15 (KLK15) has emerged as a potentially important biomarker in prostate cancer. Experimental and clinical studies have demonstrated increased expression of KLK15 in prostate cancer tissues compared with normal prostate tissue, and several investigations have reported associations between KLK15 expression levels and clinicopathological parameters such as tumor stage, Gleason score, and disease progression.

In addition to its altered expression in tumor tissues, KLK15 may also be involved in biological mechanisms related to cancer progression, including extracellular matrix degradation and modulation of signaling pathways that regulate tumor cell proliferation, migration, and invasion. These findings suggest that KLK15 may contribute to the molecular processes underlying prostate cancer development and progression.

Overall, current evidence indicates that KLK15 may represent a promising prognostic biomarker in prostate cancer. However, further research involving larger patient cohorts and integrated molecular and clinical analyses is necessary to better understand the biological role of KLK15 and to determine its potential clinical utility in prostate cancer diagnostics and prognosis.

Methodology

This study was conducted as a narrative literature review focusing on the role of kallikrein-related peptidase 15 (KLK15) as a potential biomarker in prostate cancer. Scientific articles were identified through a systematic search of major biomedical databases, including PubMed and Google Scholar, covering the period 2001–2022. The literature search was performed using combinations of the following keywords: *prostate cancer*, *KLK15*, *kallikrein-related peptidase*, *gene expression*, and *biomarkers*. Articles focusing on the molecular characteristics, expression patterns, and clinical relevance of KLK15 in prostate cancer were included in the analysis.

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