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Review

# The kallikrein-related peptidase family: Dysregulation and functions during cancer progression

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ABSTRACT

Cancer is the second leading cause of death with 14 million new cases and 8.2 million cancer-related deaths worldwide in 2012. Despite the progress made in cancer therapies, neoplastic diseases are still a major therapeutic challenge notably because of intra- and inter-malignant tumour heterogeneity and adaptation/escape of malignant cells to/from treatment. New targeted therapies need to be developed to improve our medical arsenal and counter-act cancer progression. Human kallikrein-related peptidases (KLKs) are secreted serine peptidases which are aberrantly expressed in many cancers and have great potential in developing targeted therapies. The potential of KLKs as cancer biomarkers is well established since the demonstration of the association between KLK3/PSA (prostate specific antigen) levels and prostate cancer progression. In addition, a constantly increasing number of *in vitro* and *in vivo* studies demonstrate the functional involvement of KLKs in cancer-related processes. These peptidases are now considered key players in the regulation of cancer cell growth, migration, invasion, chemo-resistance, and importantly, in mediating interactions between cancer cells and other cell populations found in the tumour microenvironment to facilitate cancer progression. These functional roles of KLKs in a cancer context further highlight their potential in designing new anti-cancer approaches. In this review, we comprehensively review the biochemical features of KLKs, their functional roles in carcinogenesis, followed by the latest developments and the successful utility of KLK-based therapeutics in counteracting cancer progression.



**Contents**



*Abbreviations:* AR, androgen receptor; B2R, kinin receptor B2; BMP, bone morphogenic protein; CDH, cadherin; DHT, dihydrotestosterone; DNA, deoxyribonucleic Acid; Dsg, desmoglein; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial to mesenchymal transition; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; HGFA, hepatocyte growth factor activator; IGFBP, insulin-like growth factor-binding protein; IL, interleukin; KLK, kallikrein-related peptidase; L1CAM, L1 cell adhesion molecule; MAPK, mitogen activated protein kinase; MCA, multicellular aggregate; miRNA, micro RNA; MMP, matrix metalloproteinase; NSCLC, non-small cell lung cancer; PAR, protease-activated receptor; PDGF, platelet-derived growth factor; PSA, prostate specific antigen; SHBG, sex hormone-binding globulin; siRNA, small interfering RNA; SNP, single nucleotide polymorphism; TGF, transforming growth factor; uPA, urokinase; UTR, untranslated region; VEGF, vascular endothelial growth factor.

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## 1. Introduction

Kallikrein-related peptidases (KLKs) are a family of fifteen homologous secreted serine endopeptidases that include KLK1 (i.e. tissue/glandular kallikrein) the namesake of the family and KLK2-15 [1–3]. In 1930, KLK1 was originally identified to be involved in the regulation of blood pressure through its kininogenase activity [4]; now, in the 21st century, it is well known that other members of this family are involved in a wide range of physiological processes, such as skin desquamation, semen liquefaction, regulation of immune response and enamel formation [2,5,6]. In addition to their physiological roles, accumulating evidence has shown that the dysregulation of KLK expression, activity or localization is frequently associated with pathological disorders, such as skin pathologies, respiratory diseases, perturbation of tooth enamel formation, neurological disorders and carcinogenesis [5–13].

In the cancer research field, this peptidase family became more well-known on the discovery of the correlation between KLK3/PSA levels in blood and prostate cancer [14]. PSA is a powerful diagnostic and tumour recurrence biomarker, even though its discriminatory power has been recently questioned [5,15]. Since then, the expression of other KLKs in neoplastic diseases has been extensively studied to extend their use as biomarkers for diagnosis and/or prognosis for other cancer types, with several KLKs being proposed to have clinical utility [5,16–20]. In addition to their possible use as indicators of cancer progression, numerous *in vitro* and *in vivo* studies highlighted their functional involvement in cancer progression [21–23]. KLKs, which are mainly expressed by cancer cells in solid tumours and secreted into the tumour microenvironment, might modulate disease progression positively or negatively via a wide range of molecular mechanisms [12]. For example, they regulate the bioactivity of several hormones and growth factors and activate cell surface receptors thereby controlling the growth of cancer cells [12,22,24]. As secreted peptidases, KLKs promote cancer cell migration and invasion through proteolysis of extracellular matrix (ECM) proteins [16,24,25]. Moreover, the KLKs are involved in chemo-resistance of cancer cells and, most importantly, in regulating interactions between cancer cells and other cell populations found in the tumour microenvironment, such as fibroblasts, endothelial cells or osteoblasts [26–29]. This functional correlation of KLKs in cancer progression opens up the opportunity to use them as therapeutic targets to counter-act tumour progression in addition to their utility as biomarkers.

In this review, after a presentation of the biochemical and biological features of the KLK family, we will comprehensively discuss their dysregulation in cancers, mechanisms of action involved in cancer progression and possible utilization as therapeutic targets for these cancers.

## 2. The human kallikrein-related peptidase family

### 2.1. KLKs at the genomic/mRNA level

The *KLK* family locus is composed of 15 genes, *KLK1-15*, located in a tandem cluster on the long arm of human chromosome 19q13.3–13.4, where they cover approximately 265 kb forming the largest continuous cluster of protease encoding genes in the human genome [2,30]. Sequence identity between the KLK genes permits the categorization of this family into two subgroups; the first identified classical KLK genes (*KLK1-3*) sharing 65.8% (*KLK2*) and 61.5% (*KLK3*) sequence similarity with *KLK1* and the new KLKs (*KLK4-15*) sharing about 34.9%–46.2% homology with *KLK1* [3]. KLKs share several genomic features. All KLK genes are formed by 5 exons highly conserved in terms of structure although each gene length varies between 4.3 and 10.5 kb. The first exon always contains the start codon and a short 5′-UTR (untranslated region), whereas the stop codon, poly-A tail and 3′-UTR are located in exon 5. The three residues forming the serine-type catalytic triad of KLKs

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