Review

Tissue kallikrein proteolytic cascade pathways in normal physiology and cancer

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Abstract

Human tissue kallikreins (KLKs or kallikrein-related peptidases) are a subgroup of extracellular serine proteases that act on a wide variety of physiological substrates, while they display aberrant expression patterns in certain types of cancer. Differential expression patterns lead to the exploitation of these proteins as new cancer biomarkers for hormone-dependent malignancies, in particular. The prostate-specific antigen or kallikrein-related peptidase 3 (PSA/KLK3) is an established tumor marker for the diagnosis and monitoring of prostate cancer. It is well documented that specific KLK genes are co-expressed in tissues and in various pathologies suggesting their participation in complex proteolytic cascades. Here, we review the currently established knowledge on the involvement of KLK proteolytic cascades in the regulation of physiological and pathological processes in prostate tissue and in skin. It is well established that the activity of KLKs is often regulated by auto-activation and subsequent autolytic internal cleavage leading to enzymatic inactivation, as well as by inhibitory serpins or by allosteric inhibition by zinc ions. Redistribution of zinc ions and alterations in their concentration due to physiological or pathological reasons activates specific KLKs initiating the kallikrein cascade(s). Recent studies on kallikrein substrate specificity allowed for the construction of a kallikrein interaction network involved in semen liquefaction and prostate cancer, as well as in skin pathologies, such as skin desquamation, psoriasis and cancer. Furthermore, we discuss the crosstalks between known proteolytic pathways and the kallikrein cascades, with emphasis on the activation of plasmin and its implications in prostate cancer. These findings may have clinical implications for the underlying molecular mechanism and management of cancer and other disorders in which KLK activity is elevated.

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Keywords: Human tissue kallikreins; Proteolytic cascades; Prostate cancer; Semen liquefaction; Skin desquamation; Skin cancer

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1. Introduction

Proteolytic cascades are implicated in many physiological processes, such as blood coagulation, food digestion, apoptosis and others [1]. A proteolytic cascade initiates when an activated protease cleaves and activates other protease zymogens that function downstream. This leads to the rapid amplification of the original signal. Serine proteases constitute a subgroup of proteases known to participate in proteolytic cascades [1]. Human kallikreins, in particular, are divided into two categories: Plasma kallikreins and tissue kallikreins [2]. Plasma kallikrein or Fletcher factor is encoded by a single gene localized on human chromosome 4q35 [3,4]. This gene is composed of 15 exons and encodes for an enzyme that releases the bioactive peptide bradykinin from high molecular weight kininogen (HMWK). Tissue kallikreins are the largest group of serine proteases in the human genome and are localized in tandem on human chromosome 19q13.4. Fig. 1 is a schematic presentation of the human tissue kallikrein locus, which is now known to consist of 15 genes [2] and one pseudogene [5]. According to the nomenclature suggested recently for human tissue kallikreins, the gene is referred to as KLK followed by the appropriate number and the protein as KLK followed by the appropriate number [6]. Most KLK genes contain one or more untranslated exons and five coding exons with identical exon–intron phases, while their 3′ untranslated region is usually variable, giving rise to mRNA variants with differing sequence lengths, that all encode for identical full-length proteins [7]. Tissue kallikrein genes all encode for serine proteases with either trypsin-like (KLK1, KLK2, KLK4, KLK5, KLK6, KLK8, KLK10, KLK11, KLK12, KLK13, KLK14, KLK15) or chymotrypsin-like (KLK3, KLK7, KLK9) activity [2].

Multiple transcriptional and post-transcriptional mechanisms control the expression, consequently, the proteolytic activity of tissue kallikreins [reviewed in [2,8]]. At the level of transcription, alternative splicing results in either the production of multiple splice variants that encode for truncated proteins or do not encode for any predicted protein sequences [reviewed in [7]]. Interestingly, distinct KLK variants display tumor-specific expression as was demonstrated for KLK5 [9–11], KLK7 [9], KLK8 [12] and KLK13 [13]. On the other hand, steroid hormones are considered as the primary regulatory mechanism of tissue kallikrein gene expression [reviewed in [8]]. However, recent data implicated genomic DNA methylation in the regulation of aberrant tissue kallikrein expression observed in tumor cells, as was described for KLK6 in breast cancer [14] and for KLK10 in prostate [15], breast [15,16], ovarian tumors [15] and in acute lymphoblastic leukemia [17]. The mRNAs encoding for tissue kallikreins are translated as inactive zymogens (preproKLK) that are either autoactivated or activated by other KLKs or different proteases. The enzymatic activity of mature (active) KLKs is further regulated by physiological inhibitors or allosterically by ions, such as Zn2+ [2].

This review focuses on known proteolytic cascades formed by enzymatically active KLKs. It is known that several KLK-encoding genes are co-expressed in specific tissues and they are co-ordinately deregulated in certain pathologies. Therefore, it is considered that multiple KLKs are involved in proteolytic cascade pathways that might be operated entirely by KLKs or may also involve the action of other proteases. Human KLKs are secreted enzymes suggesting that their biological role is related to their ability to cleave one or more substrates. Recently, in vitro studies suggested that KLKs are able to process growth factor binding proteins and cleave components.

Fig. 1. The human tissue kallikrein gene cluster. The tissue kallikrein genes (KLK) are localized in tandem on human chromosome 19q13.4 and constitute a serine protease subfamily of 15 members [2]. The aim of each arrow indicates the direction of transcription of the corresponding gene. Most KLK genes contain one or two untranslated 5′ exons (shown in white boxes). The encoded enzymes are synthesized as inactive preproKLKs. Upon proteolytic removal of the secretion (pre-) signal, activation of the proenzyme (zymogen) is required for conversion to an active (mature) enzyme. H, D, and S represent the catalytic histidine, aspartic acid and serine residues located in the active site. In this schematic representation of KLK gene structure, boxes indicate exons and lines indicate intervening introns.
of the extracellular matrix, thus, they likely play significantoles in tumor metastasis and invasion, and may promote tumor angiogenesis.

2. A tissue kallikrein cascade regulates semen liquefaction

Semenogelin I (SgI) and Semenogelin II (SgII) are secreted by seminal vesicles and represent major proteins in human semen. After ejaculation SgI, SgII and fibronectin aggregate to form a gelatinous mass that is liquefied within 5 to 20 min, resulting in release of trapped spermatozoa [18–20]. One aggregation mechanism involves the formation of disulfide bonds [21]. The process of liquefaction is mainly performed by the action of prostate-specific antigen/kallikrein-related peptidase 3 (PSA/KLK3). A highly regulated proteolytic cascade, initiated by ejaculation is responsible for the activation of proKLK3 [22,23]. At ejaculation, the sperm-rich epididymal fluid is mixed with prostatic fluid, containing KLKs 2, 3, 4, 5, 8, 11, 12, 14, 15 [expression profile is reviewed in [8] and is accompanied by secretions of seminal vesicles (i.e. SgI, SgII, fibronectin) that constitute the semen. An important feature of prostate and prostatic fluid is its high concentration of zinc ions (Zn^{2+}) [24]. Under physiological conditions, within the prostate and prostatic fluid, KLKs are inactivated by allosteric reversible binding of Zn^{2+}, as was experimentally demonstrated for: KLK2, [25]; KLK3, [23]; KLK4, [26]; KLK5, [22]; KLK8, [27]; KLK12, [28]; KLK14, [29]. After ejaculation, KLKs are reactivated due to redistribution of Zn^{2+} to semenogelins. Semenogelins bind Zn^{2+} through histidine residues at a stoichiometry of at least 10 mol Zn^{2+}/mol protein [30]. Redistribution of Zn^{2+} initiates a proteolytic cascade that leads to the activation of multiple KLKs, mainly mediated by autoactivation of KLK5 [31], and semen liquefaction.

It is well documented that KLK2 can activate proKLK3 [32–34] in a process that resembles auto-activation of KLK2 (removal of 7 amino acids) [35]. Recently, it was demonstrated that KLK4 [36], KLK15 [37] and KLK5 [22] are also able to activate proKLK3. Furthermore, KLK14 is expressed in the prostate gland and secreted in semen. It was shown that proKLK14 is activated by KLK5 [31], and mature KLK14 is able to activate proKLK5 [31]. In addition, KLK5 can efficiently degrade SgI, SgII and fibronectin [31,38], thus, promoting semen liquefaction. Similarly, KLK14 cleaves fibrinogen, and it is likely implicated in digestion of the seminal clot [29].

On the other hand, semen liquefaction is regulated by autolytic internal cleavage of the participant proteases that results in

![Fig. 2. Semen liquefaction cascade. The cascade involves several KLKs as well as plasmin [36,43,44] and TGF beta-1 [49]. In prostatic fluid, KLKs are present as latent molecules through Zn^{2+} binding. At ejaculation, mixing of prostatic fluid with epididymal and seminal vesicle fluids, results in Zn^{2+} redistribution and activation of KLKs [30]. inKLK indicates an inactive KLK. FN, fibronectin; proPlg, proplasminogen; uPA, urokinase-type plasminogen activator.](image-url)
complete inhibition of their enzymatic activities. Recently, KLK5 was shown to be responsible for the internal cleavage and inactivation of KLK3 in vitro. The resulting proteolytic fragments were analyzed by N-terminal sequencing and shown to be identical with natural peptides found in semen [22]. No other protease is known to inactivate KLK3 by proteolytic processing and production of these internal fragments (starting at KLK3 amino acid residues: R85, K182). In addition, KLK5 inactivates KLK2 [22], while KLK14 was shown to be inactivated by autolytic processing [29]. KLK11 is another kallikrein-related peptidase expressed in prostate and seminal plasma at relatively high concentrations [39]. It has been demonstrated that mature KLK12 activates proKLK11. KLK12 is auto-activated and subsequently auto-inactivated [28]. A putative physiological inactivator of mature KLK11 is plasmin [40], which is present in semen [41]. The resulting KLK11-derived proteolytic fragment is partially inactive. Approximately, 60% of KLK11 is present in a cleaved form, in which, the two resulting peptides are held together by disulfide bonds [40]. The biological role of KLK11, KLK12 and KLK8 [42] in semen has not been established yet.

In semen, a crosstalk between the plasmin and kallikrein pathways was reported [36,43,44]. Both KLK4 and KLK2 can release active plasmin, which in turn can liquefy the seminal clot and control the activity of other KLKs by proteolytic degradation. Plasmin inhibitors were shown to display an inhibitory effect on semen liquefaction [45]. Another interesting physiological pathway that is connected to human tissue kallikreins leads to the activation of TGF beta-1 present in semen, where TGF beta-1 is found as a latent complex at a very high concentration in semen as compared to other biological fluids [46–48]. Activation of TGF beta-1 in vitro proceeds in acidic pH. The acidic environment of the vagina may contribute to the activation of TGF beta-1, which may, in turn, proceed through KLK3/PSA [49] or plasmin [50]. The physiological role of TGF beta-1 is to interact with epithelial cells in the cervix and uterus, in order to activate cytokine synthesis to induce cellular and molecular changes resembling a classical inflammatory cascade. The cytokines released by seminal activation have embryotrophic properties [51]. The described cascade that leads to semen liquefaction is schematically summarized in Fig. 2.

Additionally, semen liquefaction is regulated by inhibitory serpins. The protein C-inhibitor (PCI) is considered to be the physiological inhibitor of KLK3/PSA in semen [52]. Complexes of KLK3/PSA with PCI in ejaculates are responsible for the inactivation of up to 5% of KLK3/PSA activity [52]. Formation of tertiary complexes of PCI with SgI and SgII is another way of control of the KLK3-catalyzed degradation of seminogelins [53,54]. In addition, a complex of KLK2 with PCI was detected in semen [55].

3. Involvement of a tissue kallikrein cascade in prostate cancer

The prostate tissue is known to accumulate high cellular levels of Zn$^{2+}$ [56]. In prostate cancer, the concentration of Zn$^{2+}$ falls 10 to 20 fold in prostatic tissue and prostatic fluid, respectively [57,58] as a result of down-regulation of the zinc transporter protein (hZIP1) [59,60] that is considered as a critical early event in the development of prostate cancer [59]. Additionally, down-regulation of hZIP2, another zinc transporter protein has been associated with prostate cancer development [60]. High concentrations of Zn$^{2+}$ present in the prostate inhibit the enzymatic activity of multiple kallikreins (KLK2, KLK3, KLK4, KLK5, KLK8, KLK14), as mentioned.

In prostate cancer, decrease in Zn$^{2+}$ concentration leads to increased tissue kallikrein activity, in a way that is similar to the seminal cascade described above. The important role of Zn$^{2+}$ in prostate cancer was demonstrated in vitro by showing that Zn$^{2+}$ can inhibit the invasive potential of KLK3-expressing LNCaP prostate cancer cells assessed by Matrigel assay [61]. Over-activation of KLKs leads to degradation of multiple components of the extracellular matrix (ECM) by specific KLKs and promotes tumor growth, metastasis and invasion. More specifically, KLK3 [62,63], KLK5 [38], KLK8 [64], and KLK14 [29] can efficiently cleave ECM components, such as laminin, gelatin, fibrinogen, entactin, nidogen, several types of collagen and fibronectin, as demonstrated experimentally [2]. Detailed analysis of substrate specificity by phage display approaches revealed that KLK2 cleaves ADAMTS8, cadherin-related tumor suppressor homologue precursor and collagen IX α-chain, indicating that KLK2 is directly involved in cancer progression [65]. KLK2 is a known activator of proKLK3 [32–34]. On the other hand, KLK3 activates proMMP2, which is a major ECM degradative enzyme [63]. Furthermore, KLK2 was shown to activate the zymogen of single-chain form of urokinase-type plasminogen activator (uPA) [44] in vitro and to inactivate plasminogen activator inhibitor-1 (PAI-1), the primary inhibitor of uPA, which suggests another indirect way to activate uPA-mediated proteolysis [66]. More specifically, KLK2 inactivates 6–7 mol of PAI for every mole of KLK2:PAI-1 complex formed [66]. Then, uPA binds to its cell surface receptor (uPAR) and converts plasminogen to plasmin, leading to efficient ECM degradation.

Tissue kallikreins can additionally facilitate the progression of prostate cancer by proteolytic cleavage of insulin-like growth factor binding proteins (IGFBPs). KLK2 cleaves IGFBP2, 3, 4, and 5 [67], KLK3 cleaves IGFBP3, 4 [67,68]. KLK5 was shown to cleave IGFBP1, 2, 3, 4, and 5 [22]. KLK14 cleaves IGFBP2 and 3 [29]. Cleavage of IGFBPs leads to an increased availability of insulin-like growth factors (IGFs) that bind and activate IGF receptor type 1 and this way modulate cell survival, mitogenesis, and differentiation. The interaction of KLKs with IGFBPs in vivo is considered to occur in the tumor microenvironment in the prostate. Recently, it was shown that proteinase activated receptors (PARs) are activated by KLK5, KLK6 and KLK14 [69]. Activation of PARs by KLKs may contribute to prostate cancer progression.

As mentioned previously, KLK3 can activate TGF beta-1, however, this reaction requires acidic pH [49]. Prostate cancer cells express high levels of TGF beta-1, which seems to enhance prostate cancer growth and metastasis, by stimulating angiogenesis and by inhibiting immune responses directed against...
tumor cells. Although TGF beta-1 exerts anti-proliferative and pro-apoptotic effects, prostate cancer cells acquire resistance through their down-regulation of TGF beta-1 receptors [70].

In addition, kallikrein cascades probably regulate osteoblastic metastasis of prostate cancer cells that occurs in close to 90% of prostate cancer cases and is associated with drug resistance and increased mortality. Recently, it was shown that knockout of KLK3/PSA expression by RNA interference resulted in reduced adhesion of prostate cancer cells to bone marrow epithelial cells [71]. Furthermore, KLK3/PSA can induce proliferation, activation and detachment of cultured osteoblast in vitro [49,72] and in vivo [72]. Fig. 3 summarizes the kallikrein cascade pathway involved in prostate cancer progression and metastasis, as currently established.

Finally, is should be mentioned that kallikrein cascades are additionally regulated at the level of transcription. It is well established that expression of most kallikrein genes is regulated by androgens and other steroid hormones [8]. Androgen receptor (AR) signaling, in particular, is critical at all stages of prostate cancer development. Primary prostate cancer is most often dependent on androgens, while androgen independency is associated with progression to metastatic disease and poor survival due to evolution of resistance to androgen ablation therapies [73]. Androgen-independent growth of prostate cancer may result from AR gene mutations and/or amplification, co-regulator alterations, and most often, from androgen independent activation of AR as a result of cross-talk between multiple signal transduction pathways [73,74]. Several studies have shown that expression of KLK3 is regulated by androgens, however, in advanced stages of prostate cancer, increased levels of acetylated histone 3 (H3) at the KLK3 promoter lead to androgen-independent KLK3 expression. The AR is indirectly involved in regulation of KLK3 expression in androgen-independent prostate cancer, since knockdown of AR by RNA interference results in chromatin remodeling and KLK3 silencing [75,76]. Similarly, H3 hyperacetylation results in up-regulation of KLK2 in androgen-independent prostate tumors. Taken together, these results suggest that functional selection of efficient expression of kallikrein genes may aid tumor growth in the absence of androgens [76].

4. The role of tissue kallikrein cascade in skin desquamation

The skin cascade that leads to desquamation is regulated by SPINK5 (serine protease inhibitor Kazal-type 5). Mutations in SPINK5 cause the Netherton syndrome [77], a multi-system ichthyosiform syndrome characterized by ichthyosis, erythroderma, hair shaft defects and atopic features [78].

Fig. 3. Prostate cancer progression cascade. In prostate cancer, concentration of Zn^{2+} falls dramatically to levels where KLKs become active in the prostate in a manner analogous to the semen liquefaction cascade shown in Fig. 2. KLK3 mediates binding of metastatic prostate cancer cells to bone marrow endothelial cells probably mediated by an as yet unidentified receptor indicated with a ?. ECM, extracellular matrix; IGFBP, insulin-like growth factor binding protein.
Involvement of SPINK5 is supported by the phenotype of a SPINK5(−/−) mouse that resembles the Netherton syndrome [79]. SPINK5(−/−) mouse is characterized by enzymatic hyperactivity in the stratum corneum due to the enzymatic activity of KLK5 and KLK7 [79]. In addition, mice with a premature termination codon in SPINK5 (R820X) develop severe Netherton syndrome, resulting in death a few hours after birth [80]. These mice were characterized by enhanced proteolytic processing of profilaggrin [80]. SPINK5 is a secretory serpin [81]. Proteolytic processing of SPINK5 is required for the generation of bioactive peptide inhibitors [82]. Several enzymes are involved in proteolytic processing of SPINK5 that results in the production of at least 14 polypeptides, each possessing one or a few serine protease inhibitor domains [83].

As mentioned, proKLK5 is autoactivated [31], subsequently, active KLK5 activates proKLK7 and proKLK14 [31]. KLK14 further increases the enzymatic activity of KLK5 by activating proKLK5 [31]. KLK5 was shown to cleave corneodesmosin, desmoglein 1, and desmocollin 1 [84,85], while KLK7 can cleave corneodesmosin and desmocollin 1 [84,85]. KLK14 is responsible for 50% of trypsin-like activity of the plantar stratum corneum [86]. Recently, KLK8 was reported to participate in the skin desquamation process. In KLK8(−/−) mice, a hyperkeratosis phenotype was observed [87], indicating an important role of KLK8 in skin physiology. KLK14 is inhibited by LEKTI (Lympho-epithelial Kazal-type-related inhibitor), an inhibitory peptide derived from SPINK5 [88], while SPINK5-derived peptides also inhibit the enzymatic activity of KLK5 [88–90], KLK7 [90] and KLK6 [89]. KLK6 likely plays an important role in the differentiation process of keratinocytes [91] and in psoriasis [92], Pasmatzi et al. 2007, personal communication]. In addition, BSSP (Brain and Skin Serine Protease), the mouse orthologue of KLK6 [93] is up-regulated in the mouse skin carcinogenesis model [94]. Therefore, it is considered that KLK6 participates in the skin kallikrein cascade. It should be mentioned that the enzymatic activity of KLK6 is regulated by an autocatalytic mechanism of initial autolytic activation and subsequent auto-inactivation by internal cleavage at R80 [95].

Interestingly, kallikrein-related peptidases were recently shown to play significant roles in the antimicrobial protection of skin. More specifically, KLK5 and KLK7 were shown to process the pro-form of cathelicidin (hCAP18) [96]. In accordance, it was found that, epidermal extracts of SPINK5 deficient mice display high antimicrobial activity [96]. Fig. 4 summarizes the kallikrein cascade involved in skin desquamation, as currently established.

Fig. 4. Skin desquamation cascade. Arrows depicted as double lines denote pathways inhibited by SPINK5-derived peptides. KLKs are involved in the degradation of various skin proteins [80,81] as well as in the antimicrobial protection of skin [92]. SPCs, subtilisin-like proprotein convertase; CPs, carboxypeptidases; CDSN, corneodesmosin; DSG1, desmoglein 1; DSC1 desmocollin 1.
5. Tissue kallikreins are involved in psoriasis and skin cancer

A number of common skin diseases such as, psoriasis vulgaris, seborrheic keratosis, lichen planus, and squamous cell carcinoma display high levels of KLK8 as determined by Northern blot and in situ hybridization analysis [97]. In psoriasis, KLK7 is also up-regulated compared to normal skin, in particular, in psoriatic lesions as compared to the non-lesional psoriatic skin. Both active as well as proKLK7 are detected in psoriatic lesions where conversion of proKLK7 to KLK7 occurs, and KLK7 is likely the epidermal enzyme that activates interleukin 1 beta (IL-1b) [98], while it degrades KLK7 occurs, and KLK7 is likely the epidermal enzyme that activates interleukin 1 beta (IL-1b) [98], while it degrades beta-glucocerebrosidase and acidic sphingomyelinase, two major lipid processing enzymes responsible for the basal permeability barrier function of the stratum corneum [99]. It is worth noting that, although the putative role(s) of specific KLKs in skin cancer have not been examined, tissue microarray profiling of gene expression revealed KLK6 as one of the few most highly up-regulated genes upon induction of differentiation of squamous cell carcinoma by the vitamin D3 analog EB1089 [91]. On a similar note, both KLK6 and KLK10 were among the genes that were significantly up-regulated in colon cancer cells induced to differentiate by EB1089 [100]. Further, vitamin D3 regulates the expression of KLK5, 6, 8, 10 and 13 in normal keratinocytes and constitutes an essential part of their vitamin D3-induced differentiation network [101]. These results implicate KLK6 and KLK10 in skin carcinogenesis given that impairment of cellular differentiation is an essential part of tumor development. Therefore, complex kallikrein cascades that remain to be identified are involved in the differentiation process in skin. Interestingly, immunohistochemical analysis revealed expression of KLK3/PSA in cutaneous and metastatic malignant melanomas [102]. Although causal role of KLK3/PSA in melanoma has not been established, another study suggested that the expression of KLK3/PSA in cutaneous metastases acts as a marker for the prostatic origin of metastasis [103]. Given that plasmin causes increased motility of melanoma cells [104], kallikrein cascades that lead to activation of plasmin, as demonstrated for KLK2 and KLK4 [36,43,44], are likely responsible for migration and metastasis of melanoma cells and/or other forms of skin cancer. Taken together, these results indicate that complex kallikrein cascades that remain to be described are involved in the differentiation process and carcinogenesis in skin.

6. Tissue kallikrein cascades in other tissues

It is now well established that KLK1 is involved in proteolysis that regulates various physiological processes. For example, KLK1 mediates the formation of kinin from low molecular weight kininogen (LMWK). The kallikrein–kinin system is involved in multiple physiological and pathological functions including inflammation, hypertension, renal diseases, pancreatitis and cancer. The activity of KLK1 can be inhibited by kallistatin, through the formation of a covalent link [105]. Furthermore, KLK1 is able to cleave proinsulin, low density lipoprotein (LDL), the precursor of atrial natriuretic factor, prorenin, vasoactive intestinal peptide, procollagenase, and angiotsinogen [reviewed in [106]], although release of kinin is considered the primary function of KLK1. The vasodilator, natriuretic, and diuretic effects of KLK1 are mediated by the release of eicosanoids, NO, and endothelium-derived hyperpolarizing factor [107]. Importantly, KLK1 may represent the physiological regulator of calcium metabolism as indicated by the phenotype of KLK1 knockout mouse [108].

Regulation of KLK1 activity by SPINK5 is considered to occur in the central nervous system. In the pituitary, KLKs 5–8 and 10–14 are co-expressed with SPINK5. It was further shown that KLK 4–6, 8, 13 and 14 are able to cleave and process the human growth hormone (hGH). Therefore, a complex KLK cascade is expected to exist in the human pituitary that is responsible for the proteolytic processing of hGH [88].

In addition, the co-existence of KLK3 and KLK2 in various biological fluids indicates the operation of KLK cascades. Nipple aspirate fluid [109,110], breast milk [111] and amniotic fluid [25] are examples of biological fluids known to contain both KLK2 and KLK3, while nipple aspirate fluid also contains KLK6 and KLK10 [109].

7. Conclusions

This review summarizes very recent data that show the operation of KLK enzymatic cascades in various tissues. KLKs are all secreted serine proteases, their enzymatic activity requires the proteolytic removal of a propeptide sequence, and many KLKs display parallel expression in certain tissues where they may act on diverse protein substrates. This is consistent with the presence of a KLK cascade. Sequential activation of human KLK zymogens in a way that resembles the activation of the blood coagulation cascade, food digestion cascade, etc. may underlie the regulation of multiple physiological processes, while its aberrant function could promote certain pathological conditions in the prostate tissue and in skin. An overview on our present understanding of putative crosstalks between KLK proteolytic cascade pathways and other protease-mediated pathways and their modes of regulation was presented.

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