Alternative treatments are urgently needed for prostate cancer, especially to address the aggressive metastatic castration-resistant disease. Proteolytic enzymes are involved in cancer growth and progression. The prostate produces several proteases, the most abundant ones being two members of the kallikrein-related peptidase (KLK) family, prostate-specific antigen (PSA) and KLK2. Despite the wide use of PSA as a clinical marker, the function(s) of PSA and other KLKs in prostate cancer are poorly known. Hypothetic roles of KLKs in prostate cancer include activities that may both promote and inhibit cancer growth and metastasis, including the antiangiogenic activity of PSA. Thus it may be possible to control prostate cancer growth by modulating the proteolytic activities of KLKs. PSA and KLK2 are especially attractive targets for prostate cancer treatment because of their proposed roles in tumor development and inhibition of angiogenesis in combination with their prostate selective expression. So far the number of molecules affecting selectively the activity of KLKs is limited and none of these are used to treat prostate cancer. Prodrugs that, after cleavage of the peptide part by PSA or KLK2, release active drug molecules, and PSA-targeted therapeutic vaccines have already been tested clinically in humans and the first results have been encouraging. Although KLKs are attractive targets for prostate cancer treatment, much remains to be done before their potential can be fully elucidated. The objective of this review is to address the current state of the KLKs as novel therapeutic targets for prostate cancer treatment.
INTRODUCTION

Prostate cancer is a considerable health care problem. With 900,000 new cases and about 260,000 deaths worldwide in 2008, it is the second most frequently diagnosed cancer and the sixth most common cause of cancer death in men [1]. In the UK, the lifetime risk of developing prostate cancer is estimated to be 1 in 8 (Cancer Research UK). Since the approval of prostate-specific antigen (PSA or kallikrein-related peptidase-3, KLK3) test by FDA in 1986, PSA has been the most widely used cancer marker [2]. However, extensive screening with PSA has lead to detection and unnecessary treatment of cancers that would not have surfaced clinically without screening [2]. Prostate cancer often presents as a multi-focal tumor with various degrees of aggressiveness. Because of the widespread use of screening, most prostate cancers are presently detected at an early stage and have favorable prognosis. While most patients can be cured by radical prostatectomy or radiotherapy, some are associated with side effects, and about one third of the tumors relapse [3]. Patients can be treated by androgen deprivation, but eventually most of them, and 10-20% within 5 years, become resistant to this therapy, i.e., develop castration-resistant prostate cancer (CRPC) [4]. Currently there is no cure for these cancers [5]. While CRPCs respond to some treatment modalities, the effect on survival is generally modest, i.e., some months. Therefore, it is important to develop alternative treatments that are either curative, prevent the development of CRPC and/or formation of metastatic lesions that eventually kill the patients, or to slow down the growth of small tumors, in order to prevent them from surfacing clinically within the lifetime of the patient. Proteolytic enzymes (proteases), including 15 members of the kallikrein-related peptidase (KLK) family, are potential targets for treatment of prostate cancer [6]. Despite the widespread use of PSA as a clinical marker, the function(s) of PSA and other KLKs in prostate cancer are poorly known [7]. While several KLKs may be involved in prostate cancer development, efforts to target them for treatment of prostate cancer have concerned the two major proteases produced in prostate, i.e., PSA and KLK2. Thus this review will focus mainly on these KLKs and their use as novel therapeutic targets for prostate cancer treatment.

PROTEASES IN CANCER

Since the discovery of the role of proteases in food degradation, proteases have been found to be involved in almost all biological pathways and networks, performing several essential functions in all living organisms, from fertilization and development to normal physiology [8,9]. Proteases (also called peptidases or proteolytic enzymes) may exhibit highly selective substrate cleavage or have broader specificity. About 600 human proteases, which are collectively called the degradome, representing ~2% of the whole human genome are known [10]. Among the serine proteases, KLKs form a family of 15 trypsin- and chymotrypsin-like proteases [11,12]. Protease activity is controlled by several mechanisms, including regulation of gene expression, activation of their inactive pro-forms (zymogens) either autocatalytically or by other proteases, inhibition of their activity by endogenous protease inhibitors, and phosphorylation [8,13]. Many proteases, including those of the KLK family, act in cascades or networks, which facilitates signal amplification and stringent regulation of their activity [14]. Alterations in proteolytic systems underlie several pathological conditions, including cancer, and proteases have been found to play a significant role at virtually all stages of tumor progression [9]. The roles of proteases in cancer have been widely studied since the discovery of their
role in cancer cell invasion, which is a prerequisite for tumor invasion and metastasis formation. In addition to degrading extracellular matrix proteins and adhesion molecules facilitating cell invasion, proteases have several other functions relevant for cancer, including activation of protease-activated receptors (PARs) and regulation of the activity of other signaling molecules, like kinases and growth factors [8,13,15]. Cancer has been thought to be primarily associated with increased proteolytic activity and while this is true for many proteases, some proteases exert opposite effects, such as acting as tumor suppressors by suppressing angiogenesis or inducing apoptosis [16,17].

**Expression of KLKs in prostate cancer**

The prostate produces several proteases, the most abundant ones being two KLKs, PSA and KLK2 [18]. Shaw and Diamandis reported that all 15 KLKs are expressed in the prostate at the mRNA level [18]. In tissue extracts they found, in addition to KLK2 and PSA, KLK1, -4, -5, -9, -11, -13, -14 and -15. PSA is expressed in differentiated luminal epithelial cells of the prostate and secreted into seminal fluid. The levels in extracellular fluid of the prostate are up to 2 µM or in prostate tissue 10 mg/g of tissue [18,19]. Most of this PSA is enzymatically active [19]. However, when active PSA and other KLKs reach circulation, they are rapidly inactivated by protease inhibitors that are present in vast excess in circulation. While PSA is a major constituent of seminal fluid, only a minor part of it leaks out into circulation. Interestingly, the tissue concentrations of PSA are lower in malignant than in normal prostatic epithelium and they are further reduced in poorly differentiated (high Gleason grade) tumors [20]. In spite of this, PSA is the best cancer marker presently available [2,7]. This is based on increased leakage into circulation from malignant prostatic tissue that has lost connection with the prostatic ducts [21]. The clinical use of PSA determinations has been reviewed in several recent articles [22,23]. Among the KLKs, KLK2 has attracted most interest after PSA, due to its prostate specificity and relatively high expression levels [18]. Contrary to PSA, KLK2 expression in prostate cancer is higher than in benign prostate [23,24]. The ratio between hK2 and PSA mRNA increases with increasing grade [25].

Noteworthy, single nucleotide polymorphisms (SNPs) in KLK genes have been shown to be associated with prostate cancer [26]. Some of these SNPs affect the expression levels of KLKs. However, apart from these genetic polymorphisms and hormonal regulation [11], the mechanisms behind the altered regulation of KLK expression in tumors still remains largely unsolved.

**Functions of KLKs in prostate cancer**

The suggested functions of KLKs include both those that promote and inhibit tumor growth and metastasis [7,11,12,27]. The physiological function of PSA, and perhaps also other prostatic KLKs, is to promote sperm motility by dissolving the seminal clot formed after ejaculation by cleaving semenogelins. KLKs are also able to cleave several prostate cancer related substrates, at least in vitro [11]. However, hypothetic functions based on in vitro cleavage should be interpreted with caution. In clinical studies, low PSA levels in prostate cancer tissue are associated with poor prognosis [20,28], while high PSA levels are associated with low blood vessel density [29,30]. However, the PSA concentrations in serum are sometimes increased decades before the development of otherwise detectable tumors [31,32]. This suggests that PSA may initiate or facilitate early cancer development.

Cancer cells have to acquire several biological capabilities during the multistep development of tumors described by Hanahan and Weinberg.
in *Hallmarks of Cancer* [33]. Several described or hypothesized functions of KLKs are relevant for these effects [7]. The ability to proliferate and evade growth-suppressing signals is one of the essential properties of cancer cells. Several studies suggest that PSA and other KLKs may promote the growth of prostate cancer by stimulating cell proliferation [34,35]. Furthermore, PSA has been found to promote the growth of prostate cancer xenograft tumors [34]. In contrast to these studies, Bindukumar *et al.* [37] found that subcutaneously administered PSA reduced the growth of xenograft tumors in mice. Several KLKs have been found to activate growth-factors and PARs [11,15], which lead to a wide array of responses, including promotion of cancer cell growth and invasion. In addition to increasing cell proliferation, PSA has been shown to reduce apoptosis [35], which is also essential for cancer development.

Like all tissues, tumor needs nutrients and oxygen and ability to remove waste and carbon dioxide in order to grow and survive [33]. This requires vascularization and thus tumors need to develop new blood vessels in order to grow beyond a size of 2-3 mm³ [37]. Prostate cancer grows unusually slowly after reaching this size, which corresponds to the time when it can be detected by prostate biopsy of men with elevated serum concentrations of PSA [31]. The slow growth of prostate cancer could be dependent on the antiangiogenic activity of PSA. Several studies have addressed the antiangiogenic role of PSA, which has been demonstrated in cell culture models at sub-physiological PSA concentrations [16,38,39]. In a pioneering study by Fortier *et al.*, PSA was shown to inhibit endothelial cell tube formation, growth, invasion and migration [16]. They further showed that subcutaneous administration of PSA inhibits angiogenesis in an *in vivo* model of blood vessel growth [38]. The mechanism by which PSA exerts its antiangiogenic effect is unclear. Even the dependence on enzymatic activity is controversial [38]. However, our studies strongly suggest that PSA activity is needed for the antiangiogenic activity, as the enzymatic activity of different PSA forms present in seminal fluid correlates with the antiangiogenic activity [39]. Furthermore, inhibition of PSA by small molecule inhibitors or an antibody abolishes the antiangiogenic activity [40], while the stimulation of PSA activity by peptides enhanced it [41].

Several KLKs, like PSA and KLK2, are able to degrade extracellular matrix proteins and activate other extracellular matrix degrading proteases or inactivate their inhibitors [11,14]. These studies suggest that KLKs are involved in proteolytic cascades facilitating prostate cancer growth and metastasis [14]. Indeed, PSA-treatment has been found to increase invasion of prostate cancer cells *in vitro* [42]. Other studies suggest that PSA may play a role in the development of bone metastases (reviewed in [11,43]).

Knockout studies of PSA or KLK2 have not been performed as mice and other animals used for such studies do not have genes encoding PSA or KLK2 [11]. Most studies aiming to solve the functions of KLK2, PSA, and other KLKs have utilized cancer cell lines. However, the *in vitro* growth characteristics of these cells may not necessarily predict tumorigenicity and different cell lines may show very different responses [7]. Furthermore, cancer cells grown in an isolated environment behave very differently from those in tumors and in contact with extracellular matrix and stromal cells [44]. Transgenic mice expressing PSA and/or KLK2 in the prostate have been developed. In these, neither PSA nor KLK2 have been found to initiate cancer or cause any morphological changes [45]. However, the PSA levels in these are about 1000-fold lower than those in the human prostate.

Taken together, these studies suggest that PSA and other KLKs may affect tumor growth and
perhaps even initiate cancer development. The effects of KLKs may be different at different stages of tumor growth, e.g., PSA may favor tumor development at early stages of cancer, for example by activating growth factors, but at later stages it may inhibit tumor growth by its antiangiogenic activity [7].

**KLK-TARGETED THERAPIES FOR PROSTATE CANCER**

Recently, proteases have been estimated to represent 5-10% of the potential drug targets [46,47] but the number of new approved protease inhibitors is still limited [48]. A problem with proteases as drug targets is the lack of specificity. Thus, inhibitors tend to react with similar proteases affecting a broad range of protease activities that are crucial for normal physiology. For example, lack of specificity was a major reason for the failure of early matrix metalloprotease (MMP)-inhibitors, as they also inhibited MMPs that are needed for normal tissue function, or act as tumor suppressors [46,47,17].

PSA and KLK2 are attractive targets for prostate cancer treatment because of their possible roles in tumor development, metastasis and inhibition of angiogenesis, and their prostate selective expression, which together with the lack of active forms in circulation makes systemic effects unlikely. Furthermore, as their proposed physiological function is related to liquefaction of the seminal fluid clot, their targeting is not likely to cause severe side-effects other than those related to fertility. In addition to PSA and KLK2, KLK4 is also a potential target for prostate cancer treatment [49]. KLK4 is overexpressed in prostate cancer, promotes cell proliferation and cleaves several cancer associated substrates, including PARs [11,50,51].

Several naturally occurring proteins, including serpins, Kazal-type serine protease inhibitors and α2-macroglobulin, inhibit KLKs [49,52]. However, these are rather non-specific inhibitors. So far the number of molecules affecting selectively the activity of individual KLKs is very limited and none of these are used to treat prostate cancer [6,49,52]. For PSA, both activity-stimulating and inhibiting compounds have been developed, while for KLK2 and KLK4 only inhibitors have been described (Table). Prodrugs that are activated by PSA or KLK2, and PSA-targeted therapeutic vaccines have already been tested clinically in humans and preliminary results are encouraging [53,54] (Table).

**PSA inhibitors and stimulators**

Several peptide-based or small molecule inhibitors for PSA have been described (reviewed in [6,27,49,52]). These have been found either by high-throughput screening or by rational drug design. Several antibodies that inhibit or stimulate PSA activity have also been described [55]. Some of these inhibitors have been tested in prostate cancer relevant models and found to inhibit antiangiogenic activity of PSA in a cell culture model [40], inhibit the growth of prostate cancer cell lines or exert a small inhibitory effect on xenograft tumor growth [56]. It should be noted that the specificity of these inhibitors has not been thoroughly characterized.

Since PSA shows antiangiogenic activity and, thus could inhibit development of prostatic tumors, we have been interested in molecules that stimulate the activity of PSA. By screening of almost 50,000 drug-like small molecules, we found some PSA inhibitors but did not identify compounds that stimulate PSA activity [40]. While small molecule drugs have several advantages as compared to peptides, their specificity for similar proteases is more limited. Furthermore, only 30-50% of the targets that represent an opportunity for therapeutic intervention have been suggested to be amenable to traditional small molecule approaches [57]. Thus, we have used phage-display to develop peptides,
### Summary of the major findings on different KLK targeted therapies for prostate cancer

<table>
<thead>
<tr>
<th>Strategy/target</th>
<th>Agent</th>
<th>Major outcome/therapeutic effect(^a)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>small molecules or peptide based</td>
<td>Inhibit prostate cancer cell and xenograft tumor growth; inhibit antiangiogenic activity of PSA</td>
<td>6,27,40,49, 52,56</td>
</tr>
<tr>
<td>KLK2</td>
<td>modified serpin(^b), peptide</td>
<td>Reduce xenograft tumor growth(^b)</td>
<td>63-66</td>
</tr>
<tr>
<td>KLK4</td>
<td>peptide</td>
<td>Not determined</td>
<td>68,69</td>
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<tr>
<td><strong>Stimulators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>peptide, small molecule</td>
<td>Stimulate antiangiogenic activity of PSA in cell model</td>
<td>58-62</td>
</tr>
<tr>
<td><strong>Prodrugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>PSA substrate combined with a toxic drug molecule</td>
<td>Selectively kills PSA-producing cells in vitro; selective antitumor effect on PSA-producing tumor xenografts in mice and monkeys; significant improvement of symptoms in patients with benign prostatic hyperplasia with only mild, locally limited side effects</td>
<td>73-84</td>
</tr>
<tr>
<td>KLK2</td>
<td>KLK2 substrate combined with a toxic drug molecule</td>
<td>Significant antitumor effect in tumor xenografts in vivo, but prolonged administration caused local toxic effect; less effective than similar PSA-activated prodrug</td>
<td>85</td>
</tr>
<tr>
<td><strong>Vaccination</strong></td>
<td></td>
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<tr>
<td>PSA</td>
<td>antigen (PSA), DNA-based vaccines, usually include other antigens</td>
<td>Safe in phase I and II studies, showing prostate specific T lymphocyte responses and benefit for some of the patients</td>
<td>53-54</td>
</tr>
</tbody>
</table>

\(^a\) The mentioned outcomes and therapeutic effects may be valid only for some of the agents for a given strategy and target.

\(^b\) The agent, modified serpin, not specific for KLK2.
which stimulate the activity of PSA several fold at µM concentrations [58,59]. These peptides also stimulate PSA-activity towards protein substrates but they do not affect the activity of several enzymatically or structurally related proteases (Mattsson et al., unpublished data) [59]. The use of peptides for drug discovery is a rapidly emerging field. The pharmacokinetic and other properties of peptides can be modified and they can serve as starting structures for development of peptidomimetics. We have been able to significantly improve the stability of some peptides stimulating PSA activity and created the first pseudopeptides, in which parts of the peptide have been replaced by non-peptidic structures without loss of bioactivity [60,61]. We hypothesize that modified peptides or peptidomimetic compounds based on these can be used for imaging and proof of principle studies, and eventually for treatment of prostate cancer. The peptides enhance the antangiogenic activity of PSA in cell culture models [41] but in preliminary animal studies, the first generation peptides have not shown any major effect on tumor growth (our unpublished results). This is not surprising as the peptides are quickly excreted. Using pharmacophore-based virtual screening we have recently identified the first small drug-like molecule that stimulates PSA activity [62].

**KLK2 and KLK4 inhibitors**

Since many cancers, including prostate cancer, are associated with increased activity of several proteases, inhibitors, in addition to those for PSA, have been developed for KLK2 and KLK4 for the targeting of prostate cancer. Cloutier et al. have used phage-display to screen a library of variants of α1-anti-chymotrypsin (ACT), which inhibits several proteases. They identified a modified version of ACT that showed selectivity towards KLK2 [63], but it was later found to also inhibit several other KLKs, especially KLK4, KLK5 and KLK14 [64]. This molecule, called MD-PK67b, has been shown to reduce the growth of prostate cancer xenograft tumors producing KLK2. Further clinical studies, including evaluation of safety in humans, have been initiated [64].

As our phage-display approach was successful with PSA, we also developed peptide inhibitors for KLK2 using this approach [65]. While all of the PSA-stimulating peptides were cyclic containing one or two disulfide-bridges, all the KLK2 inhibiting peptides were identified in linear peptide libraries. The identified peptides inhibited KLK2 at µM concentrations. Like with PSA-stimulating peptides, we have been able to significantly improve the stability of the KLK2-inhibitory peptides [66].

Sunflower trypsin inhibitor (SFTI), which is a 14 amino acid residue cyclic peptide structurally similar to Bowman-Birk family of serine protease inhibitors, is a potent and broad-range protease inhibitor [49,67]. Recently, SFTI has been modified to selectively and efficiently inhibit KLK4, using a combination of molecular modeling and substrate screening [68], and further in silico screening of inhibitor variants in complex with KLK4 or trypsin [69]. Although promising results with the SFTI-based KLK4 inhibitor have been obtained using ovarian cancer models [70], its effect on prostate cancer have not yet been reported.

**PSA- and KLK2-activated prodrugs**

Perhaps the most promising results concerning the use of KLKs in prostate cancer treatment have been obtained using prodrugs that are activated by PSA or KLK2. Protease-activated prodrugs are promising for targeted delivery of drugs into a specific tissue. The inactive prodrug consists of a toxic drug molecule conjugated to a peptide. The prodrug is activated in the target tissue through cleavage of the peptide moiety
by a specific protease leading to release of the active drug molecule [71,72]. Thus, the effect of the drug is directed to a specific tissue. PSA and KLK2 are well suited as prodrug activators as they have highly tissue specific expression, i.e., significant amounts of active PSA and KLK2 are found only in the prostate [6,18].

Several PSA-activated prodrugs have been developed using peptide sequences that are highly selective for PSA [73,74]. Drug molecules conjugated to these peptides include doxorubicin [73-75], vinblastine [76], 5-fluorodeoxyuridine [77], thapsigargin [78] and paclitaxel [79]. A doxorubicin conjugated prodrug L-377,202 selectively killed PSA-producing human prostate cancer cells in vitro and was 15 times more effective than conventional doxorubicin at inhibiting the growth of human prostate tumor xenografts in vivo [74]. Another PSA-activated prodrug, PRX302, with the bacterial toxin precursor proaerolysin, showed selective antitumor effect on PSA-producing tumor xenografts in mice, caused extensive damage to PSA-producing prostate cells in monkeys and showed no toxicity in other tissues [80]. These two PSA-activated prodrugs have been taken to phase I and II clinical trials, where both were well tolerated, although L-377,202 caused neutropenia at higher doses [75]. Intraprostatic injections of PRX302 lead to significant improvement of symptoms in patients with benign prostatic hyperplasia while only mild, locally limited side effects were reported [81].

Recent studies of PSA-activated prodrugs report utilization of cell penetrating peptides to deliver drugs inside prostate cancer cells [82], development of prodrug modifications using e.g. albumin as a drug carrier [83] and synthesis of fusion peptides with multiple specificities to target the drug effect to the cells that express specific receptors [84]. A thapsigargin-based prodrug has been developed for KLK2 [85]. A prodrug with a KLK2 peptide substrate conjugated to the thapsigargin analog, L12ADT, showed a significant antitumor effect in human prostate tumor xenografts in vivo, but prolonged administration caused local toxic effects [85]. Moreover, the antitumor effect was only modest when compared to a similar PSA prodrug with thapsigargin.

**PSA-targeted therapeutic vaccines**

Prostate cancer is considered an attractive target for development of therapeutic vaccines as it expresses several prostate-specific proteins and generally grows very slowly. Indeed, several vaccination strategies have been established, some of which target PSA (reviewed in [53,54]). Usually these vaccines also target other antigens in order to improve the immune response. For PSA, viral and DNA-based vaccines have been used, both encoding PSA and, usually, other antigens. These vaccines have been found to be safe in phase I and II studies, showing prostate specific T lymphocyte responses and, at least in some cases, some benefit for the patients [53,54]. It seems that these vaccines would be especially beneficial for patients with early-stage disease but results from phase III studies are not available yet.

**CONCLUSIONS**

PSA is an established marker for prostate cancer and several other KLKs are potential markers. As circulating PSA level is often used as a surrogate marker for tumor burden in preclinical and clinical studies [73-76,80,83], and more importantly to monitor relapse in patients, it would be important to address whether KLK targeted therapies could affect PSA levels also otherwise than by affecting the volume of the PSA producing tumor tissue. This is possible as PSA-targeted activity modulators and vaccination may affect, through several mechanisms,
the circulating PSA levels and also the detection of PSA by immunoassay. While in prodrug studies PSA seems to be a good marker for tumor burden, the therapy has also been found to induce initial leakage of PSA into circulation [81], perhaps because of tissue destruction.

While conclusive evidence for the roles of the KLKs in prostate cancer development is still lacking, KLKs expressed in the prostate are likely to have functional role(s) making them potential targets for treatment of prostate cancer. We have proposed that PSA promotes the growth of small tumors, but may inhibit development of large tumors at the stage when new blood vessels are needed [7]. In addition to PSA and KLK2, some other KLKs, like KLK4, are also potential targets for prostate cancer treatment. However, these KLKs have been less studied and their expression is not as restricted to the prostate as that of KLK2 and PSA. Therefore development of treatment based on these is more challenging. While several inhibitors for PSA and KLK2, and stimulators for PSA have been developed, their efficacy has not yet been tested in higher primates or humans. Some of these compounds have been promising in cell culture and mouse xenograft tumor models. However, the models used so far have several limitations and do not reflect the complexity of human prostate cancer. Furthermore, the specificity of the compounds has not been fully elucidated. Prodrugs that are activated by PSA or KLK2 have been tested clinically in humans with encouraging preliminary results. It is foreseen that these prodrugs, along with vaccines targeting PSA, may be the first KLK-based treatment modalities for prostate cancer. In conclusion, KLKs are attractive targets for prostate cancer treatment, but much remains to be done before their potential can be fully harnessed to treat prostate cancer.

DISCLOSURES

Ulf-Håkan Stenman holds patents for KLK-activity modulating peptides. Hannu Koistinen and Johanna Mattsson have nothing to disclose.

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