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REVIEW ARTICLE

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Target molecules in specific immunotherapy against prostate cancer

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Abstract Recent advances in molecular biology and tumor immunology have allowed us to identify genes encoding human cancer-related antigens and their peptides that are recognized by cytotoxic T lymphocytes (CTLs). Although these advances have been preceded by studies on melanoma antigens, prostate cancer is another target candidate for specific immunotherapy. Several prostate tissue-specific antigens can be target molecules in specific immunotherapy for prostate cancer. The distribution of prostate tissue-specific antigens is more localized than that of melanoma-related antigens. Prostate-specific antigen (PSA) is available as an evaluation indicator of clinical course. In addition, epithelial cancer-related antigens are also applicable for prostate cancer patients. These lines of evidence suggest that prostate cancer is the best candidate for specific immunotherapy among the various types of epithelial cancers. A number of epitope peptides which have the potential to generate prostate cancer-reactive CTLs have been identified to date, and clinical trials targeting these molecules have been conducted. In this article, we review prostate cancer-related antigens and their epitope peptides, which have potential for use in the immunotherapy of prostate cancer patients, and we introduce the current status of clinical trials of specific immunotherapy targeting these molecules.

Key words Prostate cancer · Immunotherapy · Cytotoxic T lymphocytes (CTLs) · Peptide · Vaccine

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Introduction

Recent advances in molecular biology and tumor immunology have allowed us to identify genes encoding human cancer-related antigens, and their peptides that are recognized by cytotoxic T lymphocytes (CTLs), in patients with various types of cancers.[1,2] These advances have been preceded by studies on melanoma antigens, for the following reasons: (1) the identification of predominant antigens, such as cancer-testis and melanocyte-differentiation antigens; (2) the easy preparation of tumor-infiltrating lymphocytes; (3) the relatively high frequency of melanoma-reactive CTLs in the peripheral blood mononuclear cells (PBMCs) of patients, and (4) the preferential expression of major histocompatibility complex (MHC) class II molecules on melanoma. As a consequence, several treatment modalities, including vaccination with melanoma antigens or their peptides, adoptive immunotherapy with melanoma-reactive T cells, and gene therapy with recombinant viruses, have been applied to melanoma patients.[3–6]

Prostate cancer is one of the most common cancers in elderly men.[7] Although hormone ablation therapy can temporarily palliate patients with prostate cancer, the progression to hormone-refractory prostate cancer (HRPC) is inevitable in most cases. Therefore, the development of novel therapeutic modalities for HRPC is needed, and specific immunotherapy is one candidate. Tissue-specific antigens, which are expressed in the normal prostate, can be target molecules for specific immunotherapy for prostate cancer. In addition, immunotherapy for prostate cancer seems to have some advantages compared with that for melanoma. First, prostate-specific antigen (PSA) is available as an evaluation marker of clinical course.[8] Second, the distribution of prostate tissue-specific antigens is more localized than that of melanocyte-differentiation antigens. Especially, immune response to prostate-related antigens can be considered as tumor-specific in patients with recurrent metastases after radical prostatectomy. In addition, epithelial cancer-related antigens are also applicable for immunotherapy for prostate cancer. These lines of evidence

Table 1. A list of prostate-related antigen-derived peptides recognized by T cells

Antigen	HLA restriction	Peptide position	Amino acid sequence	Reference no.
PSA	HLA-A2	146–154	KLQCVDLHV	9
		141–150	FLTPKKLQCV	10
		154–163	VISNDVCAQV	10
		154–163 (1Y)[a]	YISNDVCAQV	11
	HLA-A3	162–170	QVHPQKVTK	12
	HLA-A24	152–160	CYASGWGSI	13, 14
		248–257	HYRKWIKDTI	14
PSMA	HLA-A2	4–12	LLHETDSAV	15
		711–719	ALFDIESKV	16
		27–35	VLAGGFFLL	17
	HLA-A24	178–186	NYARTEDFF	18
		227–235	LYSDPADYF	18
		624–632	TYSVSFDSL	19
PAP	HLA-A2	299–307	ALDVYNGLL	20
	HLA-A24	213–221	LYCESVHNF	21
	Class II	199–213	GQDLFGIWSKVYDPL	22
	Class II	228–242	TEDTMTKLRELSELS	22
PSCA	HLA-A2	14–22	ALQPGTALL	23, 24
		105–113	AILALLPAL	24
		7–15	ALLMAGLAL	25
		21–30	LLCYSCKAQV	25
KLK4	DRB1*0404	155–169	LLANGRMPTVLQCVN	26
	DRB1*0701	160–174	RMPTVLQCVNVSVVS	26
	DPB1*0401	125–139	SVSESDTIRSISIAS	26

[a] Valine at the first position of the PSA 154–163 peptide is replaced by tyrosine
PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; PAP, prostatic acid phosphatase; PSCA, prostate stem-cell antigen; KLK4, kallikrein 4

suggest that prostate cancer is the best candidate for specific immunotherapy among the various types of epithelial cancers. In this article, we review prostate cancer-related antigens and their epitope peptides, which have the potential to generate prostate cancer-reactive CTLs, and we introduce the current status of clinical trials of specific immunotherapy targeting these molecules.

Prostate-related antigens

For specific immunotherapy, it is necessary to determine the antigens and eptiope peptides that can be recognized by the immune responses. Prostate cancer-related antigens can be mainly divided into two groups: prostate-related antigens, and epithelial cancer-related antigens. The former group includes PSA, prostate-specific membrane antigen (PSMA), prostatic acid phosphatase (PAP), prostate stem-cell antigen (PSCA), and kallikrein (KLK) 4. A list of prostate-related antigen-derived peptides recognized by T cells is shown in Table 1.

PSA

PSA is a kallikrein-like serine protease, and human PSA has a high degree of homology with human pancreatic kallikrein.[8,27] Immunoperoxidase staining indicates that PSA is found in the cytoplasmic portion of prostate cancer cells. PSA is a potential target for immunotherapy against prostate cancer, and has been applied as an evaluation marker for the clinical course.[8]

Several HLA-A2-binding PSA-derived peptides have been reported to have the potential to generate peptide-specific or prostate cancer-reactive CTLs. Xue et al.[9] revealed that a synthetic nonamer peptide, corresponding to residues 146–154 of PSA and containing a canonical HLA-A2-binding motif, could induce peptide-specific CTLs from the PBMCs of a normal HLA-$A2^+$ donor. Since then, this peptide has been shown to induce peptide-specific and PSA-reactive CTLs from prostate cancer patients.[28] Correale et al.[10] identified other HLA-A2-binding PSA-derived peptides, PSA 141–150 and PSA 154–163 peptides, which are capable of eliciting peptide-specific CTLs cytotoxic to prostate cancer cells. In addition, a modified PSA 154–163 peptide, in which valine at the first position was replaced by tyrosine, was shown to be more immunogenic in inducing prostate cancer-reactive CTLs compared with the parental PSA 154–163 peptide.[11]

Two HLA-A24-binding PSA peptides were reported to generate peptide-specific CTLs. Gotoh et al.[13] revealed that the PSA 152–160 peptide is immunogenic in the HLA-A*2402/K^b-transgenic mouse to generate peptide-specific and HLA-A*2402-restricted CTLs. We recently reported that both the PSA 152–160 and PSA 248–257 peptides are immunogenic in HLA-$A24^+$ healthy donors and prostate cancer patients.[14] These peptide-stimulated PBMCs of HLA-$A24^+$ prostate cancer patients showed cytotoxicity against prostate cancer cells in an HLA-A24-restricted manner. Interestingly, IgG specific to the PSA 248–257 peptide was detected in 80% and 50% of healthy donors and prostate cancer patients, respectively. This peptide seems to be recognized by T-cell and B-cell immunity.

An oligopeptide, longer than 9-mer or 10-mer, was reported to generate tumor-reactive CTLs. Correale et al.[12] revealed that a 30-mer PSA 141–170 peptide, which contains both the PSA 141–150 and PSA 154–163 peptides for the HLA-A2 molecules and an additional CTL epitope, the PSA 162–170 peptide, for the HLA-A3 molecules, has the potential to generate HLA-A2-restricted or HLA-A3-restricted CTLs cytotoxic to PSA-expressing target cells, respectively. These studies provide evidence that oligopeptides can be useful for peptide-based cancer vaccines.

Immunotherapy using mRNA encoding PSA has been investigated. Heiser et al.[29] tested the efficacy of autologous dendritic cells (DCs) which were transfected with mRNA encoding PSA. PSA RNA-transfected DCs generated PSA-specific CTLs. This protocol can bypass the identification of PSA peptides binding to each HLA class I molecule. They also showed that autologous DCs transfected with RNA amplified from microdissected tumor cells are capable of stimulating CTLs against a broad set of unidentified and critical prostate-specific antigens.[30] The polyclonal CTL responses, generated using amplified tumor RNA-transfected DCs, contained responses against PSA. These CTLs, which recognized not only tumor cells but also self-antigens expressed by benign prostate tissue, were exclusively specific for PSA, suggesting a central role of PSA in the immune response to prostate tissue-specific antigens.

PSA has been applied to immunotherapy for prostate cancer patients as a vaccination with protein and PSA-encoding gene. Meidenbauer et al.[31] reported that vaccination with recombinant human PSA and granulocyte macrophage-colony stimulating factor (GM-CSF) induced PSA-reactive T cells in almost half of the prostate cancer patients tested. Only 1 of 18 patients was a clinical responder. The vaccine had stimulatory effects on this patient's immune system, but post-vaccine immune recovery could not be correlated to progression-free survival in this small cohort of patients with prostate cancer. Cavacini et al.[32] reported that vaccination with vaccinia- or fowlpox-expressed PSA resulted in determinant spreading in the antibody responses against prostate cancer-related antigens other than PSA. Gulley et al.[33] conducted a phase I study of a vaccine using recombinant vaccinia virus expressing PSA in patients with metastatic androgen-independent prostate cancer. There was no significant treatment-related severe toxicity, whereas the proportion of PSA-specific T cells increased after vaccination, and these patients' T cells could lyse PSA-expressing tumor cells in vitro. In addition, PSA RNA-transfected DCs were also used for a phase I trial, in which it was reported that the induction of PSA-specific T-cell responses was consistently detected in all patients, and that vaccination was associated with a significant decrease in the level of PSA in 6 of 7 subjects.[34]

PSMA

PSMA is a membrane-bound glycoprotein that was identified using monoclonal antibody (mAb) 7E11.C5.[35] Immunohistochemical findings indicate that PSMA is a marker of epithelial cells of the prostate.[36] In contrast to PSA and PAP, which are secreted proteins, PSMA is an integral membrane protein.[35] This expression is increased in association with prostate carcinoma, particularly in HRPC.

Several PSMA peptides that are immunogenic in HLA-$A2^+$ patients have been reported. Tjoa et al.[25] reported that a PSMA 4–12 peptide induced peptide-specific CTLs when the PBMCs of HLA-$A2^+$ prostate cancer patients were stimulated with autologous DCs prepulsed with the PSMA peptide. Murphy and colleagues (Murphy et al.;[16] Tjoa et al.;[37] and Murphy et al.[38]) revealed that an HLA-A2-binding PSMA 711–719 peptide had the potential to decrease the levels of PSA in prostate cancer patients when adoptively transferred with this PSMA peptide-pulsed DCs. In addition, a PSMA 27–35 peptide was shown to induce CTLs that were effective at recognizing prostate tumor cells expressing the HLA-A2 and PSMA molecules.[17] Regarding the HLA-A24-binding PSMA peptides, Horiguchi et al.[18] reported that the in-vitro stimulation of the PBMCs of an HLA-$A24^+$ healthy donor with DCs pulsed with either a PSMA 178–186 or PSMA 227–235 peptide elicited peptide-specific and PSMA-recognizing CTLs. We[19] also recently reported that a PSMA 624–632 peptide was immunogenic in both HLA-$A24^+$ healthy donors and prostate cancer patients, and that the PSMA 624–632 peptide-stimulated PBMCs showed cytotoxicity against prostate cancer cells in an HLA-A24-restricted manner.

Clinical trials using PSMA peptides have been extensively conducted by Murphy's group. They carried out a phase I clinical trial assessing the administration of autologous DCs pulsed with HLA-A0201-binding PSMA 4–12 and PSMA 711–719 peptides.[16,37,38] The participants were divided into five groups – receiving peptides alone (PSMA 4–12 or PSMA 711–719 peptide), autologous DCs, or DCs pulsed with either the PSMA 4–12 or PSMA 711–719 peptide. An average decrease in PSA was detected only in the last group, i.e., those receiving DCs pulsed with the PSMA 711–719 peptide. In this study, these PSMA peptides and peptide-pulsed DCs were intravenously administered to patients.

PAP

PAP gives rise to a 354-amino-acid (aa) polypeptide.[39] A mAb with specificity for PAP can stain only normal prostate and prostate cancer cells. PAP, therefore, appears to be a good target for immunotherapy against prostate cancer.

Peshwa et al.[20] reported that the PAP 299–307 peptide is immunogenic, and has the potential to generate peptide-specific and HLA-A2-restricted CTLs cytotoxic to prostate cancer cells. Inoue et al.[21] revealed that the PAP 213–221 peptide induced peptide-specific CTLs from HLA-A*2402-positive healthy donors and prostate cancer patients. Interestingly, they demonstrated that PAP is expressed in some epithelial cancer cell lines, and that PAP-specific CTLs can show cytotoxicity to them. However, McNeel et al.[22] tried to identify T-helper epitopes from PAP. Both the PAP 199–

213 and PAP 228–242 peptides were found to have the potential to generate PAP-recognizing $CD4^+$ T cells, whereas the restriction molecules of HLA class II were not determined.

Several clinical trials targeting PAP have been conducted. Small et al.[40] performed a phase I clinical trial of patients with HRPC using autologous DCs which were preloaded with recombinant fusion protein PAP linked to GM-CSF (Provenge; Dendron, Seattle, WA, USA). Thirty-eight percent of the treated patients developed immune responses to PAP; 3 patients had a more than 50% decline in their level of PSA, and another 3 patients had a 25% to 49% decrease in their level of PSA. However, Fong et al.[41] reported that immunization with recombinant rat or human PAP in complete Freund adjuvant (CFA) leads to a significant antibody response, but does not generate CTL or result in autoimmune prostatitis. In contrast, immunization with recombinant vaccinia expressing human PAP, but not rat PAP, generated a CTL response and tissue-specific prostatitis in the absence of detectable PAP-specific antibodies. Subsequently, they conducted a phase I clinical trial using DCs pulsed with recombinant mouse PAP as a tumor vaccine. Six of the 21 treated patients developed T-cell immunity to human PAP following vaccination, and showed clinical stabilization of their previously progressing prostate cancer.[42] These results demonstrate that xenoantigen immunization can break tolerance to a self-antigen in humans, resulting in a clinically significant antitumor effect.

PSCA

PSCA is a recently identified prostate-specific antigen with 30% homology to stem cell antigen 2, a member of the Thy-1/Ly-6 family of glycosylphosphatidylinositol (GPI)-anchored cell surface antigens.[43] PSCA encodes a 123-aa protein with a carboxyl-terminal GPI-anchoring sequence and multiple N-glycosylation sites. A secreted form of PSCA exists. PSCA expression is highly upregulated in both androgen-dependent and androgen-independent prostate cancers,[43] suggesting that this antigen could be a good candidate for specific immunotherapy for patients with HRPC. In addition, immunotherapy targeting PSCA is promising for the treatment of patients with bone metastases, as the expression of PSCA in prostate cancer increases with tumor progression, and is higher in metastases than in primary tumors.[44]

Several PSCA-derived peptides, capable of inducing prostate cancer-reactive CTLs, were identified. The PSCA 14–22 peptide was reported to be capable of generating a PSCA-specific T-cell response from an HLA-$A*0201^+$ patient with metastatic prostate cancer.[23] The PSCA 14–22 and PSCA 105–113 peptides were revealed to be immunogenic in HLA-$A*0201^+$ prostate cancer patients, and induced HLA-A*0201-restricted and prostate cancer-reactive CTLs.[24] We[25] also identified that the PSCA 7–15 and PSCA 21–30 peptides effectively induce HLA-A2-restricted and prostate cancer-reactive CTLs from prostate cancer patients. These two PSCA peptides were suggested to be immunogenic in several HLA-A2 subtypes, including HLA-A*0201, -A*0206, and -A*0207. To our knowledge, an HLA-A24-binding PSCA-derived peptide having the potential to induce prostate cancer-reactive CTLs has not been identified.

No clinical trials using PSCA-derived peptides have been conducted. However, Saffran et al.[45] reported that PSCA is a target candidate of humoral immunity. They examined the antitumor effect of anti-PSCA mAbs in human prostate cancer xenograft mouse models by using androgen-dependent and androgen-independent cell lines. The administration of anti-PSCA mAb inhibited the formation of subcutaneously inoculated or orthotopic xenograft tumors. In addition, the administration of anti-PSCA mAbs led to the retardation of established orthotopic tumor growth, and the inhibition of metastasis to distant sites. Furthermore, human PSCA-expressing established xenograft tumors were completely regressed in a large proportion of animals by the administration of anti-PSCA mAb conjugated with maytansinoid.[46] These results suggest that PSCA is an attractive target for immunotherapy against prostate cancer, especially for humoral immunity. Several reports indicate that PSCA is overexpressed in pancreatic adnocarcinoma and transitional cell carcinoma.[47,48]

KLK4

Kallikrein (KLK) 4 is a recently described antigen that is specifically expressed in both normal and tumor tissues in the prostate.[49] KLK4 was defined to be a serine protease and a member of the tissue kallikrein gene family. Although no epitope peptides for CTLs have been identified, Hural et al.[26] reported the presence of $CD4^+$ T cells specific for KLK4 in the PBMCs of normal individuals. They showed that in-vitro stimulation with overlapping KLK4-derived peptides induced T cells with different specificity, and they identified three different CD4 epitopes. These epitopes, KLK4 155–169, KLK4 160–174, and KLK4 125–139 peptides, were restricted by HLA-DRB1*0404, HLA-DRB1*0701, and HLA-DPB1*0401 class II alleles, respectively. They also demonstrated that $CD4^+$ T cells specific for these KLK4 epitopes existed in PBMCs from multiple male donors.

Epithelial cancer-related antigens for prostate cancer

Several antigens, which are not prostate tissue-specific but are highly expressed in prostate cancer, have been identified. One of them is parathyroid hormone-related protein (PTH-rp), which is a protein produced by prostate carcinoma and other epithelial cancers, and is a key agent in the development of bone metastases.[50] Francini et al.[51] reported that the PTH-rp 59–68 and PTH-rp 165–173 peptides, having binding affinity to HLA-A*0201 molecules, could induce peptide-specific CTLs from healthy donors, and that these PTH-rp peptide-specific CTLs could kill PTH-rp^+ and

Table 2. Clinical trials of specific immunotherapy for prostate cancer

Target antigens	Protocol	Results	Reference no.
Prostate-related antigen			
PSA	Vaccination with recombinant human PSA plus GM-CSF	Induction of PSA-reactive T-cell responses (50%) Clinical response (1/18)	31
	Vaccination with vaccinia or fowlpox virus	Evidence of determinant spreading of antibody to prostate cancer-related antigens other than PSA	32
	Vaccination with recombinant viruses	Induction of prostate cancer-reactive T cells	33
	Vaccination with PSA RNA-transfected DCs	Induction of PSA-specific T-cell response in all patients (100%) Decrease in PSA (6/7)	34
PSMA	Vaccination with DCs pulsed with PSMA 4–12 or PSMA 711–719 peptide	Decrease in PSA by vaccine with DCs pulsed with PSMA 711–719 peptide	16, 37, 38
PAP	Vaccination with fusion protein PAP linked to GM-CSF	Induction of response to human PAP (38%) Decrease in PSA	40
	Vaccination with rat or human PAP in CFA	Successful induction of antibody, but no induction of CTL response	41
	Vaccination with DCs pulsed with recombinant mouse PAP	Induction of T-cell response to human PAP (6/21)	42
Epithelial cancer-related antigens	Vaccination of peptides derived from epithelial cancer-related antigens after confirmation of peptide-specific CTL precursors in the PBMCs	Increased CTL response to administered peptides (4/10) Induction of IgG reactive to peptides administered (7/10) Partial response (1/10); stable disease (5/10)	56

GM-CSF, granulocyte-macrophage-colony stimulating factor; DCs, dendritic cells; CFA, complete Freund adjuvant; CTL, cytotoxic T lymphocyte; PBMCs, peripheral blood mononuclear cells

HLA-A2$^+$ prostate and breast carcinoma cell lines. In addition, they demonstrated that these two peptides were also able to elicit a strong antitumor PTH-rp-specific CTL response in HLA-A*0201-transgenic mice, without any side effects. Another antigen, which is overexpressed in hormone-refractory metastatic prostate cancer, is the polycomb group protein enhancer of zeste homolog 2 (EZH2).[52] The amounts of EZH2 mRNA and EZH2 protein are increased in metastatic prostate cancer. In addition, clinically localized prostate cancers that express higher concentrations of EZH2 show a poor prognosis. These lines of evidence suggest that EZH2 could be a good target for immunotherapy against prostate cancer.

Because prostate cancer is an epithelial cancer, some epithelial cancer-related antigens are also expressed in prostate cancer. It was reported that cancer-testis antigens, including MAGE-A12 and GAGE-1, -2, -8; and NY-ESO-1, were expressed in prostate cancer.[53,54] In addition, Zhang et al.[55] examined the distribution of 30 kinds of tumor antigens in normal and prostate cancer tissues, and found that GM2, TF, Tn, sTn, hCGβ, MUC1, MUC2, KSA, and PSMA were preferentially expressed in prostate cancer tissues. On the other hand, Noguchi et al.[56] reported that prostate cancer cell lines and tissues were positive for the expression of SART-2, SART-3, and p56^{lck} proteins. Both SART-2 and SART-3 are widely expressed in various types of cancers, and p56^{lck} is preferentially expressed in metastatic cancer.[2] HLA-A24$^+$ HRPC patients were vaccinated with peptides selected from 14 kinds of peptide candidates (maximum of four peptides) after confirmation of peptide-specific CTL precursors in prevaccination PBMCs. An increased CTL response to both peptide and cancer cells was observed in four of ten patients. Anti-peptide IgG was detected in the post-vaccination sera of seven of ten patients. One patient achieved a partial response with an 89% decrease in PSA, and stable disease was observed in five of ten patients. These results indicate that peptides from epithelial cancer-related antigens can be useful for the specific immunotherapy of HRPC. Clinical trials of specific immunotherapy for prostate cancer are summarized in Table 2.

Conclusion

As described in this article, prostate cancer appears to be the best target for specific immunotherapy among the various types of epithelial cancers. In particular, prostate tissue-specific antigens seem to be useful, just as is the case with melanocyte-differentiation antigens for melanoma. We consider the establishment of an effective immunotherapy against prostate cancer to be a touchstone by which immunotherapy can be recognized as a useful treatment modality for epithelial cancers. It is our hope that the study of immunotherapy for prostate cancer can provide a breakthrough in the development of an effective therapeutic cancer vaccine.

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