Abstract. Prostate cancer (PCa) poses a high risk to older men and is the second most common type of male malignant tumor in western developed countries. Additionally, there is a lack of effective therapies for PCa at advanced stages. Novel treatment strategies such as adenovirus-mediated gene therapy and virotherapy involve the expression of a specific therapeutic gene to induce death in cancer cells, however, wild-type adenoviruses are also able to infect normal human cells, which leads to undesirable toxicity. Various PCa-targeting strategies in adenovirus-mediated therapy have been developed to improve tumor-targeting effects and human safety. The present review summarizes the relevant knowledge regarding available adenoviruses and PCa-targeting strategies. In addition, future directions in this area are also discussed. In conclusion, although they remain in the early stages of basic research, adenovirus-mediated gene therapy and virotherapy are expected to become important therapies for tumors in the future due to their potential targeting strategies.

1. Introduction

Adenoviruses. Adenoviruses are linear and non-enveloped double-stranded DNA viruses. The length of genomic DNA is ~36 Kb, and the gene is divided into coding and non-coding regions. The coding region contains five early transcription units (E1A, E1B, E2, E3 and E4), two delayed transcription units (IX and Iva2) and one late transcription unit (L1-L5). A close association exists between E1 (E1A and E1B) and viral replication. E3 is associated with virus immune evasion and is not important for viral replication. Adenoviruses are divided into seven subgroups, A-G, and human adenoviruses encompass 52 types, of which Ad2 and Ad5 are widely employed in adenovirus studies (1,2).

Adenovirus-mediated gene therapy and virotherapy. Gene therapy and virotherapy involve the introduction of therapeutic genes into tumor cells in order to treat tumors. Adenoviruses that mediate anti-tumor therapy include two types of recombinant adenoviruses, which are replication-deficient adenoviruses (RDAds) and conditional replication adenoviruses (CRAds).

The E1 region consists of the E1A gene, E1B-19 kDa (K) gene and E1B-55K gene. These genes regulate viral replication and the gene expression of other early genes. An adenovirus with deletion of E1 is termed a RDAd due to its lack of self-replication (3-9). In adenovirus-mediated gene therapy, the adenovirus is used as a gene vector to induce the expression of therapeutic genes to inhibit tumor growth. However, the lack of a tumor-targeting effect is problematic; RDAds for infection of specific tissue or tumor cells efficiently deletes partial genes that are essential to adenoviral replication in normal cells but are unnecessary for adenoviral replication in tumor cells.

2. Development of a prostate-specific promoter/enhancer to induce expression of therapeutic genes and viral replication that is limited to specific tissues or tumor cells

3. Modification of adenovirus capsid proteins to construct an adenovirus combined with specific cell surface receptors

4. Deletion of partial genes that are essential to adenoviral replication in normal cells but are unnecessary for adenoviral replication in tumor cells

5. Clinical research on adenovirus-mediated gene therapy and virotherapy for prostate cancer

6. Future directions

7. Conclusion
may be transduced into normal cells and cause unpredictable cytotoxicity (10). CRAdS, also referred to as oncolytic adenoviruses, is one method used in virotherapy and these viruses are capable of self-replication and the delivery of therapeutic genes (11,12). CRAdS contain the E1A region that has a key role in viral self-replication. After CRAdS infect tumor cells, the virus is able to replicate itself to generate progeny viruses and induce the expression of therapeutic genes. The tumor cells subsequently die and release CRAdS and their progeny viruses, which further infect adjacent tumor cells. However, CRAd-infected normal cells survive as CRAd cannot replicate itself inside these cells (13). The following three major strategies are employed to construct these two types of recombinant adenovirus to enhance tumor-targeting: Development of a tumor/tissue-specific promoter/enhancer to induce expression of therapeutic genes and viral replication that is limited to specific tissue or tumor cells (14); modification of adenovirus capsid proteins to construct an adenovirus combined with specific cell surface receptors that efficiently infects specific tissues or tumor cells, with the deletion of partial genes that are essential to adenoviral replication in normal cells but unnecessary for replication in tumor cells (15); and deletion of partial genes that are essential to adenoviral replication in normal cells but unnecessary for replication in tumor cells (16).

2. Development of a prostate-specific promoter/enhancer to induce expression of therapeutic genes and viral replication that is limited to specific tissues or tumor cells

RDAdS or CRAdS with a prostate-specific promoter or enhancer may exert anti-tumor effects in prostate cancer (PCa) cells only via expression of the therapeutic gene or by oncolysis. Evidence of recombinant adenoviruses with a prostate-specific promoter or enhancer is presented in Table I.

Prostate-specific antigen (PSA). PSA is present in the cytoplasm of prostatic duct epithelial cells and prostate gland cells, and PSA expression has been observed in normal prostate tissues and PCa cells. PSA is the primary biomarker used to monitor PCa. PSA is also employed to screen patients with PCa and monitor the recurrence of PCa following treatment (17-21). CV706 is the first oncolytic adenovirus with the PSA promoter. The PSA promoter drives the expression of E1A and causes the oncolytic adenovirus to replicate in PSA-positive PCa cells and induce oncolysis. However, the ability to self-replicate was low in PSA-negative PCa cells, and its progeny virus production was also low (22,23). In phase I clinical trials, treatment with CV706 was applied to patients with local PCa following radiotherapy, and the results demonstrated a marked decrease in PSA levels and a satisfactory antitumor effect (24). Wang et al (25) developed a recombinant adenovirus that expressed β-glucuronidase (βG) under the control of the PSA promoter (Ad/PSAP-GV16-βG). The prodrug DOX-GA3, N-[4-doxorubicin-N-carbonyl (oxymethyl) phenyl] O-β-glucuronaryl carbimate, is converted into toxic DOX by βG. The results of an MTT assay indicated that the oncolytic virus induced significant oncolysis in LNCaP PCa cells, however, the same effect was not observed in PSA-negative DU145 PCa cells. In addition, intravenous injection of Ad/PSAP-GV16-βG and treatment with DOX-GA3 efficiently inhibited the growth of LNCaP cell xenograft tumors in nude mice. These results demonstrated the efficacy of the PSA promoter in adenovirus-mediated gene therapy and virotherapy against PSA-producing PCas.

Probasin (PB). PB is a member of the lipocalin superfamily and is a type of ligand transporter. PB is isolated from the nucleus of the dorsal lateral lobe of the rat prostate and is located in the ducts and nucleus of prostate epithelial cells (26,27). As such, PB exhibits tissue specificity, and experiments have demonstrated that a PB promoter may be regulated by androgens and drive the expression of foreign genes in PCa cells in vitro and prostate tissue in vivo (28). Trujillo et al (29) developed a CRAd with PB and Rous sarcoma virus (RSV) promoters that drove the expression of the E1 gene, and NIS:cdNA-bGH polyA that replaced the E3 region (CRAd Ad5PB_RSV-NIS). In vitro, infection of LNCaP PCa cells by the CRAd led to virus replication and cytolysis, and the release of infective viral particles. However, androgen receptor (AR)-negative PC-3 cells (PCa cell line) and Panc-1 cells (pancreatic cancer cell line) infected by the CRAd demonstrated no virus replication or cytolysis. In vivo, intratumoral injection with the CRAd and administration of therapeutic 131Iodine in nude mice carrying LNCaP cell xenograft tumors markedly inhibited tumor growth and increased nude mouse survival rates. As the RSV promoter induces the expression of therapeutic genes, it may be employed to target cancer cells and normal cells and tissues, and the RSV promoter has a low targeting effect (10).

The above results demonstrate that the PB promoter is a prostate-specific promoter. The RDAd (Ad-ARR2PB-Bax) expressed the apoptotic Bcl2-associated X (Bax) gene driven by a PB promoter containing two androgen response elements (ARR). Following infection of LNCaP cells with Ad-ARR2PB-Bax, androgen dihydrotestosterone induced Bax-mediated apoptosis. This antitumor effect of RDAd was also observed in LNCaP xenograft tumors (30). These results indicate that adenoviruses with a PB promoter may employed to target AR-positive PCa.

Prostate-specific membrane antigen (PSMA). PSMA is a type 2 intrinsic membrane protein on prostatic epithelial cells that is homologous with the serum transferrin receptor. PSMA is primarily expressed in PCa cells and is highly expressed in PCa and during metastasis (31-37). Gao et al (38) constructed a recombinant adenovirus that expressed human sodium iodide symporter (hNIS) driven by the PSMA promoter (Ad. PSMApro-hNIS). Compared with the recombinant adenovirus containing a cytomegalovirus (CMV) promoter (Ad. CMV-hNIS), expression of the hNIS gene induced by the PSMA promoter was highly prostate-specific in different LNCaP cell lines, particularly in the androgen-independent C81 LNCaP cell line. The antitumor effect of radiodine therapy was improved in C81 cell xenografts in nude mice that received PSMA promoter-driven hNIS transfection compared with CMV promoter-driven hNIS transfection. A recombinant adenovirus, combined with the prodrug 5-fluorocytosine, was developed to express the cytosine deaminase (CD) gene driven by a PSMA promoter and enhancer [Ad-PSMA (E-P)-CD]. This treatment caused PSMA-producing PCa cells (LNCaP and CL-1) to regress and efficiently inhibited the growth of
| Author, year      | Therapeutic type | Promoter | Enhancer | Therapeutic genes | Adenovirus | Combination | Experiment type | Result                                                                 | (Refs.) |
|------------------|------------------|----------|----------|-------------------|------------|-------------|----------------|------------------------------------------------------------------------|---------|
| Chen et al, 2001 | Virotherapy      | NA       | PSA      | NA                | NA         | Ad-PSE-E1A  | In vitro/vivo    | Specific inhibition of tumor/tumor cell growth                         | (22)    |
| Wang et al, 2016 | Gene therapy     | PSA      | NA       | βG                | Ad/PSAP-GV | Prodrug DOX-GA3 | In vitro/vivo    | Specific inhibition of tumor/tumor cell growth                         | (25)    |
| Trujillo et al, 2010 | Virotherapy | PB/RSV   | NA       | NIS               | Ad5PB-RSV-NIS | Radioiodine therapy | In vitro/vivo    | Specific inhibition of tumor/tumor cell growth                         | (29)    |
| Andriani et al, 2001 | Gene therapy | ARR(2)PB | NA       | Bax               | Av-ARR(2)PB-Bax | NA          | In vitro/vivo    | Specific inhibition of androgen-dependent tumor/tumor cell growth       | (30)    |
| Gao et al, 2014 | Gene therapy     | PSMA     | NA       | NIS               | Ad.PSM-Apro-hNIS | Radioiodine therapy | In vitro/vivo    | Specific inhibition of CRPC/CRPC cell growth                           | (38)    |
| Zeng et al, 2007 | Gene therapy     | PSMA     | NA       | CD                | Ad-PSMA(E-P)-CD | Prodrug 5-FC | In vitro/vivo    | Specific inhibition of tumor/tumor cell growth                         | (39)    |
| Fan et al, 2010  | Virotherapy      | DD3      | NA       | IL-24             | Ad/DD3-E1A-IL-24 | NA          | In vitro/vivo    | Specific inhibition of tumor/tumor cell growth                         | (43)    |
| Mao et al, 2010  | Virotherapy      | DD3      | NA       | SATB1-shRNA       | Ad-hTERTp-E1a, OBP301 | NA          | In vitro/vivo    | Specific inhibition of LNCaP cell growth                               | (44)    |
| Huang et al, 2008 | Virotherapy     | hTERT    | NA       | NA                | Ad-hTERTp-E1a, OBP301 | NA          | In vitro/vivo    | Specific inhibition of tumor/tumor cell growth                         | (59)    |
| Zhang et al, 2006 | Gene therapy     | hTERT    | NA       | HSV-TK            | Ad-hTERT-HSV-TK | Gangcyclovir | In vitro/vivo    | Specific inhibition of tumor/tumor cell growth                         | (60)    |
| Bhang et al, 2011 | Virotherapy     | PEG-3    | NA       | MDA-7/interleukin (IL)-24 | Ad.PEG-E1A-MDA-7 | NA          | In vitro/vivo    | Specific inhibition of advanced tumor/tumor cell growth                | (61)    |
| Greco et al, 2010 | Virotherapy      | PEG-3    | NA       | MDA-7/interleukin (IL)-24 | Ad.PEG-E1A-MDA-7 | Ultrasound contrast agents, microbubbles | In vitro/vivo    | Specific inhibition of advanced tumor/tumor cell growth                | (62)    |
| Canales et al, 2006 | Virotherapy    | BSP      | NA       | NA                | Ad-BSP-E1a | Small molecule inhibitors to telomerase with oligonucleotide-based agents, Taxotere® | In vitro/vivo    | Specific inhibition of androgen-independent tumor/tumor cell growth   | (72)    |
| Author, year       | Therapeutic type | Promoter | Enhancer | Therapeutic genes | Adenovirus | Combination | Experiment type | Result                                                                 |
|-------------------|------------------|----------|----------|-------------------|------------|-------------|----------------|------------------------------------------------------------------------|
| Li et al, 2011    | Virotherapy      | BSP      | NA       | NA                | Ad-BSP-E1a | NA          | In vitro/vivo    | Specific inhibition of androgen-independent intraosseous tumor/tumor cell growth (73) |
| Yu et al, 1999    | Virotherapy      | hK2      | hK2, hK2/PSA | NA                | Ad5-hK2e-hK2p-E1A, Ad5-PSE-E1A-hK2e-hK2p-E1B | NA          | In vitro         | Specific inhibition of PSA-positive tumor cell growth (79)             |
| Koeneman et al, 2000 | Gene therapy    | OC       | NA       | HSV-TK            | Ad-OC-HSV-TK | NA          | In vitro/vivo    | Specific inhibition of androgen-independent metastatic tumor/tumor cells (85) |
| Matsubara et al, 2001 | Gene therapy   | OC       | NA       | NA                | Ad-OC-E1a  | Valacyclovir | I/II clinical trial | One of six patients with hormone-refractory metastatic prostate cancer has exhibited a significant antitumor effect (87) |
| Hsieh et al, 2002 | Virotherapy      | OC       | NA       | NA                | Ad-OC-E1a  | Vitamin D3  | In vitro/vivo    | Specific inhibition of androgen-independent metastatic tumor/tumor cells (88) |
| Dash et al, 2010  | Virotherapy      | OC       | NA       | NA                | Ad-OC-E1a  | NA          | In vitro/vivo    | Specific inhibition of androgen-independent metastatic tumor/tumor cells (89) |
| Sarkar et al, 2015 | Virotherapy      | CCN1/ CYR61 | NA     | MDA-7/ IL-24     | Ad.jCCN1-    | Small molecule inhibitors of Mcl-1, BI-97D6 | In vitro/vivo    | Specific inhibition of advanced tumor/tumor cell growth (92)             |
| Ding et al, 2012  | Virotherapy      | DD3      | NA       | PTEN              | Ad.DD3 .Δ55-PTEN | NA          | In vitro/vivo    | Specific inhibition of tumor/tumor cell growth (115)                    |
| Lu et al, 2013    | Virotherapy      | PSA, PSMA, MMTV | NA | NA                | AdPSAE1, AdPBE1, AdMMTVE1 | NA          | In vitro/vivo    | AdPSAE1 achieves the most promising oncolysis (126)                     |
| Therapeutic type | Author, year | Experiment type | Result | Gene promoters | Combination type | (Refs.) |
|------------------|-------------|----------------|--------|----------------|-----------------|---------|
| PB               | Wilks et al., 2002 | Hormone ablation therapy | Specific inhibition of androgen-independent tumor cell growth | NA | Androgen | NA, not applicable; PB, probasin; RSV, Rous sarcoma virus; NIS, sodium iodide symporter; ARR, androgen response element; Bax, Bcl2-associated X; PSMA, prostate-specific membrane antigen; CRPC, castration-resistant prostate cancer; CD, cytosine deaminase; 5-FC, 5-fluorocytosine; DD3, differential display code 3; IL, interleukin; SATB homeobox 1; shRNA, short hairpin RNA; hTERT, human telomerase reverse transcriptase; PEG-3, progression elevated gene 3; MDA, melanoma differentiation-associated protein; BSP, bone sialoprotein; hK2, human kallikrein 2; OC, osteocalcin; HSV-TK, herpes simplex virus thymidine kinase; PTEN, phosphatase and tensin homolog; MMTV, mouse mammary tumor virus; SV40, simian virus 40. |
| SBP              | Zhang et al., 2013 | Gene therapy | Specific inhibition of androgen-independent tumor cell growth | SV-40 | Ad-hTERT-PNP | (128) |
| SV40             | Xie et al., 2001 | Gene therapy | Specific inhibition of androgen-independent tumor cell growth | hK2 | AdyK2 | (129) |
| Ad5-SV40-PNP     | Mao et al., 2008 | Adenovirus | In vitro/vivo | hK2 | Androgen | (127) |

CL-1 xenograft tumors. These results indicate that the PSMA promoter may be an important prostate-specific promoter for adenovirus-mediated treatment of PSMA-positive PCa cells (39).

**Prostate cancer gene 3 (PCA3).** PCA3 is a type of long non-coding RNA that is one of the PCa-specific markers discovered in recent years. Overexpression of PCA3 occurs in >95% of primary PCa and metastatic cancer specimens, and is not observed in other normal tissues (40-42). Fan et al (43) developed two plasmids containing the differential display code (DD3) of PCA3 promoter and the PSA promoter (pG3L3-DD3 and pG3L3-PSA, respectively). Luciferase activity demonstrated that the DD3 promoter and the PSA promoter exhibited similar activity in the LNCaP PCa cells. However, the DD3 promoter exhibited ~2-fold higher activity compared with the PSA promoter in DU145 PCa cells. In non-PCa cell lines, the DD3 promoter exhibited a lower activity compared with the PSA promoter. Therefore, the results indicated that the DD3 promoter is more PCa-specific. Furthermore, two oncolytic adenoviruses were developed to express interleukin (IL)-24 driven by the DD3 promoter and the PSA promoter (Ad.DD3-E1A-IL-24 and Ad.PSA-E1A-IL-24, respectively). In vitro and in vivo, the antitumor effect of Ad.DD3-E1A-IL-24 was higher compared with Ad.PSA-E1A-IL-24. Further experiments demonstrated that the PCa specificity of the DD3 promoter was higher.

Mao et al (44) reported that the expression of the E1A gene driven by the DD3 promoter of Ad-DD3-E1A occurred in LNCaP PCa cells and not in non-PCa cell lines (BT549 and RWPE2). These results indicate that the DD3 promoter may be useful as a PCa-specific promoter with applications for PCa-targeting by adenovirus-mediated therapy.

**Human telomerase reverse transcriptase (hTERT).** Telomeres maintain cell chromosome stability and cell activity. Telomere activity is inhibited in normal cells, however, telomerase is reactivated in the majority of human tumor tissues (45-48). High activity of TERT occurs in PCa. However, the activity of TERT is low or absent in normal or benign prostatic hyperplasia tissue (49-52). OBP-301 is an oncolytic virus that contains the hTERT promoter (53-55). OBP-401 is an oncolytic virus that expresses green fluorescent protein (GFP) under control of the hTERT promoter (55-58). When OBP-401 was employed to infect different PCa cell lines (PrEC, PrSC, LNCaP, PC3 and DU145), the expression of GFP occurred in LNCaP, PC3 and DU145 PCa cell lines, but not in PrEC and PrSC normal prostate cell lines. Intratumoral injection with OBP-301 significantly inhibited LNCaP cell xenograft tumors in nude mice. In addition, histological and immunohistochemical analyses demonstrated diffuse oncolysis of tumor cells and the expression of the E1A protein in the tumors (59). Zhang et al (60) developed a recombinant adenovirus that expressed the herpes simplex virus-thymidine kinase (HSV-TK) gene driven by the hTERT promoter (Ad-hTERT-HSV-TK). Ad-hTERT-HSV-TK, combined with ganciclovir (GCV), effectively suppressed the growth of LNCaP cell xenograft tumors in nude mice. These results demonstrate that the hTERT promoter is a PCa-specific promoter that may be useful in improving the PCa-targeting effect.
Progression elevated gene-3 (PEG-3). PEG-3 was identified through subtraction hybridization of E11 or E11-NMT cell xenograft tumors during the search for genes involved in malignant transformation and tumor progression. Various trans-acting factors activate PEG-3 in a number of human cancers, including PCa, breast and skin cancer, with limited activity observed in normal tissues. Therefore, PEG-3 exhibits tumor specificity (61-65). Sarkar et al (66) constructed an oncolytic adenovirus expressing the melanoma differentiation-associated protein 7 (MDA-7)/IL-24 driven by the PEG-3 promoter (Ad.PEG-E1A-mda-7). Prostatic epithelial cells infected by Ad.PEG-E1A-mda-7 exhibited no expression of E1A and MDA-7, however, expression was observed in LNCaP, DU145 and PC-3 PCa cell lines infected by Ad.PEG-E1A-MDA-7. Ad.PEG-E1A-MDA-7 also markedly inhibited the growth of DU145 cell xenograft tumors in vitro and in vivo (66). Greco et al (62) combined Ad.PEG-E1A-MDA-7 with ultrasound contrast agents (microbubbles) to improve the PCA-targeting effect of the oncolytic adenovirus via ultrasonic guidance. The results demonstrated that microbubble/Ad.MDA-7 complexes markedly reduced the tumor burden in DU145 cell xenograft tumors in nude mice. These results indicate that use of the PEG-3 promoter in the recombinant adenovirus selectively induces the expression of therapeutic genes in PCa.

Bone sialoprotein (BSP). BSP, an acid glycoprotein that is a member of the small integrin-binding, N-linked glycoproteins family, is abundant in the extracellular matrix and is secreted by osteoblasts and osteoclasts (67,68). BSP is associated with the occurrence and development of tumors, and high expression of BSP has been reported in breast cancer, PCa, lung cancer, melanoma and other types of bone metastases (69-71). Canales et al (72) developed an oncolytic virus containing the BSP promoter (Ad-BSP-E1a). The oncolytic adenovirus, combined with small molecule antisense oligonucleotide-based inhibitors (GRN163) and Taxotere® (Sanofi A.S.A., Paris, France), markedly inhibited the growth of the C42B PCa cell line. In addition, Li et al (73) reported that the oncolytic adenovirus (Ad-BSP-E1a) inhibited C42B growth and also decreased PSA levels in vitro. In vivo, the oncolytic adenovirus suppressed the growth of subcutaneous and intraosseous xenograft tumors of the C42B PCa cell line in nude mice (73). These results indicate that the recombinant adenovirus with the BSP promoter has PCa specificity and that CRAds with the BSP promoter have potential for the oncolysis of advanced PCa.

Human kallikrein 2 (hK2). hK2 is a serine protease that is member of the hK family that consists of a highly conserved sequence. hK2 is primarily produced by prostate epithelial cells (74,75) and is also expressed in breast, ovary, testis and other tissues, however, its expression is higher in prostate tissue (75-77). A previous study demonstrated that the hK2 protein was expressed in PSA-negative prostate tumors and in each tumor cell (78). As a result, in addition to PSA, hK2 is considered to be an important marker of PCa. An oncolytic adenovirus mutant that expressed E1A under control of the hK2 promoter/enhancer was referred to as CV763. A study demonstrated that replication of CV763 was notably high in PSA-positive prostate tumor cells, but was attenuated in PSA-negative and non-prostate tumor cells. CV763 containing the PSA enhancer was referred to as CV764, and exhibited a higher therapeutic index for PSA-positive LNCaP PCa cells (79). The above results indicate that the adenovirus with the hK2 promoter may improve PCa specificity.

Osteocalcin (OC). OC, which is secreted by osteoblasts, is a marker of bone metabolism, and bone is the most common metastatic tissue of advanced PCa. The activity of osteoblasts is closely associated with bone metastasis of tumors. Therefore, OC produced by osteoblasts is also associated with the progression of PCa bone metastasis. Compared with PSA, OC has a high sensitivity and specificity for diagnosing PCa bone metastasis (80-84). Koeneman et al (85) constructed an RDAd that expressed HSV-TK driven by the OC promoter (Ad-OC-TK). Ad-OC-TK combined with GCV effectively destroyed PCa cell lines in vitro and PCa xenografts in vivo, in subcutaneous and bone sites. In phase I clinical trials, patients with local metastasis of PCa were treated with Ad-OC-TK. The results demonstrated that all patients reported an absence of severe side effects, and PCa cell death was observed during treatment (86). Matsubara et al (87) reported that an oncolytic adenovirus with the OC promoter effectively inhibited the growth of PCa cell lines (LNCaP, C4-2 and ARCaP). In addition, in vivo, this oncolytic adenovirus also markedly suppressed intraosseous xenograft tumors, and PSA levels decreased without a subsequent rebound. Furthermore, combination with vitamin D3 significantly enhanced the antitumor effect of Ad-OC-E1A (88). These results indicate that the recombinant adenovirus containing the OC promoter may be a promising treatment strategy for advanced PCa.

CCN1/ Cyr61 gene. Elevated expression of the CCN1/Cyr61 gene occurs in various cancers, such as advanced PCa, due to oncogenic transformation, and this expression increases with the aggressiveness of the transformed cells (89-91). Sarkar et al (92) developed a recombinant adenovirus that expressed MDA-7/IL-24 driven by a truncated (t)CCN1 promoter (Ad.CCN1-CTV-m7). The MDA-7/IL-24 gene under the control of the tCCN1 promoter of Ad.tCCN1-CTV-m7 exhibited high expression in PCa cells. In vitro, the Ad.tCCN1-CTV-m7 exerted a dose-dependent killing effect on PCa cells without injury to normal prostatic epithelial cells. In vivo, Ad.tCCN1-CTV-m7 significantly suppressed PCa xenograft tumors in transgenic Hi-Myc mice when combined with ultrasound-targeted microbubble-destruction. Furthermore, Ad.tCCN1-CTV-m7 combined with small molecule inhibitors of Mcl-1, and BI-97D6, improved apoptosis and tumor growth suppression in Hi-myc mice. These results indicate that the adenovirus with the tCCN1 promoter improved the PCa-targeting effect of the adenovirus and the ability of other treatments to destroy PCa cells.

Combination of promoter and/or enhancer. The combination of a promoter and/or enhancer is a common targeting strategy used to improve PCa specificity of recombinant adenoviruses (Table II). Lee et al (93) developed an RDAd with a prostate-specific enhancing sequence (PSES) promoter that consisted of a PSA enhancer and PSMA enhancer (Ad-PSES-luc). Luciferase analysis demonstrated that high
Table II. Evidence for prostate cancer-targeting strategy of combination of promoter and/or enhancer.

| Author, year | Therapeutic type | Promoter | Enhancer | Therapeutic genes | Adenovirus | Combination | Experiment type | Results | (Refs.) |
|--------------|-----------------|----------|----------|-------------------|------------|-------------|-----------------|---------|--------|
| Lee et al, 2002 | Gene therapy | NA | PSES, PSA/PSMA | NA | Ad-PSES-luc | NA | In vitro/vivo | Demonstrates that PSES exhibits specificity for PSA/PSMA-positive prostate cancer | (93) |
| Cheng et al, 2006 | Virotherapy | TARP | PSES, PSA/PSMA | NA | Ad(I/PPT-E1A) | NA | In vitro/vivo | Specific inhibition of prostate cancer/cells | (95) |
| Cheng et al, 2004 | Gene therapy | TARP | PSES, PSA/PSMA | NA | Ad(I/PPT-Luc) | NA | In vitro/vivo | Demonstrates that PSES exhibits specificity for prostate cancer | (98) |
| Kraaij et al, 2007 | Gene therapy | PB | PSA | NA | Ad5-PSA74-Pb4-EC | NA | In vitro/vivo | Demonstrates specificity for prostate cancer | (99) |
| Liu et al, 2010 | Virotherapy | PB | PSA | NA | Ad5 PSE/PBN E1-AR | Radiation therapy | In vitro/vivo | Specific inhibition of AR-positive prostate cancer/cells | (100) |
| Li et al, 2005 | Virotherapy | NA | PSES, PSA/PSMA | NA | AdE4PSESE1a | NA | In vitro/vivo | Specific inhibition of PSA/PSMA-positive prostate cancer/cells | (130) |
| Jimenez et al, 2010 | Virotherapy | NA | PSES, PSA/PSMA | TRAIL | Ad-E4PSESE1a-TRAIL | NA | In vitro/vivo | Specific inhibition of androgen-independent prostate cancer/cells | (131) |

NA, not applicable; PSES, prostate-specific enhancing sequences; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; TARP, T-cell receptor γ-chain alternate reading frame protein; PB, probasin; AR, androgen receptor; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.
expression of the luciferase gene occurred in PSA- and PSMA-expressing PCa cell lines in vitro following infection with Ad-PSES-luc. In vivo, when Ad-PSES-luc was injected into the prostate, high luciferase activity occurred in the prostate, but not in other tissues. The expression of T-cell receptor γ-chain alternate reading frame protein (TARP) is specific to prostate epithelial cells and PCa cells. The PPT promoter containing the PSA enhancer, the PSMA enhancer and the TARP promoter demonstrates a high specificity for the prostate. The H19 insulator is introduced upstream of the PPT sequence to protect the PPT promoter from transcriptional interference from adenoviral backbone sequences (94-97). Cheng et al (98) constructed an adenovirus vector that expressed the luciferase gene under control of the PPT promoter with the H19 insulator [Ad(I/PPT-Luc)]. The I/PPT promoter generated high activities in testosterone-deprived PCa cells and PC-346C PCa cell orthotopic xenograft tumors in nude mice. Cheng et al (95) also reported that an oncolytic adenovirus [Ad(I/PPT-EIA)] that infected hormone-dependent and hormone-independent PCa cell lines induced expression of the E1A protein, virus replication and cytolysis in vitro, and the growth of LNCaP cell xenograft tumors in nude mice was markedly inhibited in vivo. Furthermore, the recombinant adenovirus with the PPT promoter, a two-step transcriptional amplification (TSTA) system, amplified [Ad(PPT/TSTA-Luc)]-enhanced prostate-specific transcriptional activity (97), and the Ad(I/PPT-EIA) with a reintroduced full-length E3 region [Ad(I/PPT-EIA, E3)] improved the cytopathic effect and suppression of PCa growth (96). Kraaij et al (99) reported that replication of an adenovirus with the PSA enhancer and the PB promoter (Ad5-PSA74-Pb4-EC) was observed in PCa cells. In addition, an oncolytic adenovirus with the PSA enhancer and the PB promoter (Ad5 PSE/PBN E1-AR), combined with low/high dose-rate radiation, exerted marked adenovirus-mediated PCa cell death (100). Furthermore, Yu et al (79) developed an oncolytic adenovirus with the PSA enhancer and the hK2 promoter (CV764). Compared with CV763, CV764 enhanced the inhibitory effects on PCa in vitro and in vivo. These results demonstrate that a recombinant adenovirus combined with an enhancer and/or promoter produces a higher targeting effect and enhancement of the antitumor effects, which may indicate that adenoviruses combined with other treatments may improve PCa specificity and the suppression of growth.

3. Modification of adenovirus capsid proteins to construct an adenovirus combined with specific cell surface receptors for infection of specific tissue or tumor cells efficiently deletes partial genes that are essential to adenoviral replication in normal cells but are unnecessary for adenoviral replication in tumor cells

Recombinant adenoviruses with modification of adenovirus capsid proteins may enhance the ability to infect PCa cells by binding to the novel receptors on the surface of the cells. Evidence of recombinant adenoviruses with modification of the adenovirus capsid proteins is presented in Table III.

Species C adenoviruses, such as Ad2 and Ad5, infect cells via Coxsackie-adenovirus receptors (CARs) on the cell surface (101). Different levels of CAR expression have been observed in various tumor types and CAR expression is downregulated in a number of tumors, such as CAR-negative PCa, which results in inefficient Ad-mediated therapeutics (101). Incorporation of an arginine-glycine-aspartic acid (RGD) peptide into the HI loop of the adenovirus fiber knob allows adenoviruses to infect CAR-negative PCa cells via cell-surface integrin αvβ3/5, which is expressed by all PCa cell lines (101). Suzuki et al (101) developed an adenovirus mutant with an RGD-fiber modification (Ad5-Δ24RGD). Compared with an adenovirus mutant without the RGD-fiber modification (Ad5-A24), Ad5-A24RGD exhibited a higher infection ability and an anti-PCa effect. A number of studies involving recombinant adenoviruses with RGD-fiber modification further confirmed that the RGD-modified adenovirus may enhance the PCa-targeting effects in vitro and in vivo (102-105).

The generation of chimeric adenoviruses, in which one adenovirus fiber knob is replaced with a different adenovirus fiber knob, may alter the orientation of the adenovirus and enhance transduction targeting to improve the tumor cell infection efficiency. Azab et al (106) constructed a recombinant adenovirus in which the fiber knob was replaced with an Ad.3 fiber knob, and this construct expressed the MDA-7/IL-24 gene (Ad.5/3-CTV). Compared with Ad.5-CTV, Ad.5/3-CTV exhibited a higher efficiency in inhibiting the viability of low-CAR human PCa cells in vitro, and also potently suppressed low-CAR PCa cell xenograft tumors in vivo. It has been reported that the Ad.3 receptor is highly expressed in tumor cells (107). Ad.5/3 infected the tumor cells via the Ad.3 receptor instead of CAR, and, therefore, it was able to infect tumor cells with low or no expression of CAR (107-109). Systemic treatment with Ad.5 is associated with serious hepatotoxicity and systemic toxicity (110). Xu et al (110) developed a chimeric oncolytic adenovirus that expressed soluble transforming growth factor β receptor II-Fc fusion protein (sTβRFe), the chimeric oncolytic adenovirus in which seven hypervariable regions of Ad.5 were substituted with the corresponding sequence of Ad48 (mHAd.sTβRFe). In vivo, mHAd.sTβRFe retained an inhibitory effect on PC-3 PCa bone metastases in nude mice, and also reduced the hepatotoxicity and systemic toxicity to indirectly improve the tumor-targeting effect. Serotype 35 adenoviruses infect cells through cell surface CD46 receptors, which are widely expressed on normal and cancer cells (111). Kim et al (111) constructed a novel chimeric recombinant adenovirus expressing monomeric red fluorescence protein (mRFP)/modified HSV-TK (ttk) (Ad5/35PSES. mRFP/ttk), which was driven by PSES and featured the serotype 35 fiber knob on the serotype 5 backbone. This chimera improved the cell infection efficiency, and the PSES enhanced the PCa-targeting effect. In vitro, replication assays demonstrated that Ad5/35PSES.mRFP/ttk replicated in PSES-positive PCa cells (LNCaP and CWR22rv) but not in PSES-negative PCa cells (DU145 and PC3). Evaluation of the cytotoxic activity demonstrated that Ad5/35PSES.mRFP/ttk killed LNCaP and CWR22rv cells more effectively. In addition, the chimeric oncolytic adenovirus Ad5/35E1αPSESE4 also effectively killed PSA/PSMA-positive PCa cells in the peripheral circulation (112).

4. Deletion of partial genes that are essential to adenoviral replication in normal cells but are unnecessary for
### Table III. Evidence for prostate cancer-targeting strategy of modification of adenovirus capsid proteins.

| Author, year | Therapeutic type | Method of modification of the fiber knob | Therapeutic genes | Adenovirus | Combination | Experiment type | Result | (Refs.) |
|--------------|------------------|------------------------------------------|-------------------|------------|-------------|----------------|--------|---------|
| Suzuki et al., 2001 | Virotherapy | Incorporation of an RGD peptide into the HI loop of the fiber knob | NA | Ad5-Δ24RGD | NA | In vitro/vivo | Specific inhibition of prostate cancer/cells | (101) |
| Cody et al., 2013 | Virotherapy | Incorporation of an RGD peptide into the HI loop of the fiber knob | OPG | Ad5-Δ24-sOPG-Fc-RGD | NA | In vitro/vivo | Specific inhibition of progression of prostate cancer bone metastases | (102) |
| Shen et al., 2016 | Virotherapy | Incorporation of an RGD peptide into the HI loop of the fiber knob | NA | AxdAdB3-F/RGD | NA | In vitro/vivo | Specific inhibition of CAR-deficient prostate cancer/cells | (105) |
| Azab et al., 2014 | Virotherapy | Replacing the Ad the Ad.3 fiber knob | MDA-7/IL-24 | Ad.5/3-PEG-E1A-MDA-7/IL-24, Ad.5/3-CTV | NA | In vitro/vivo | Specific inhibition of advanced prostate cancer/cells | (106) |
| Hakkarainen et al., 2009 | Virotherapy | Replacing the Ad 5 fiber knob with the Ad.3 fiber knob | NIS | Ad5/3-Δ24-hNIS | Radioiodine therapy | In vitro/vivo | Specific inhibition of prostate cancer/cells | (108) |
| Xu et al., 2014 | Virotherapy | Replacing seven hypervariable regions of Ad5 hexon with the Ad48 | sTGβRIIFc | Ad5/48,sTGβRIIFc, mHAd.sTGβRIIFc | NA | In vitro/vivo | Specific inhibition of progression of prostate cancer bone metastases | (110) |
| Kim et al., 2013 | Virotherapy | Insertion of serotype 35 fiber knob into the serotype 5 backbone | sFLT3L ligand and mRFP/ttk | Ad5/35PSES, mRFP/ttk | NA | In vitro | Specific inhibition of PSES-positive prostate cancer cells | (111) |
| Hwang et al., 2016 | Virotherapy | Insertion of serotype 35 fiber knob into the serotype 5 backbone | NA | Ad5/35E1aPSESE4 | NA | In vitro/vivo | Specific inhibition of PSES-positive circulating prostate tumor cells | (112) |

RGD, arginine-glycine-aspartic acid; NA, not applicable; OPG, osteoprotegerin; CAR, Coxsackie-adenovirus receptor; MDA, melanoma differentiation-associated protein; IL, interleukin; NIS, sodium iodide symporter; sTGβRIIFc, soluble transforming growth factor β receptor II-Fc fusion protein; sFLT3L, soluble fms-related tyrosine kinase 3 ligand; mRFP, monomeric red fluorescence protein; ttk, modified herpes simplex virus thymidine kinase; PSES, PSES, prostate-specific enhancing sequences.
5. Clinical research on adenovirus-mediated gene therapy

Currently, viral gene therapy is an area of increasing interest in the field of tumor therapy. Adenovirus-mediated gene therapy and virotherapy are among the most common research areas in viral gene therapy. As these therapies have demonstrated satisfactory anti-PCa effects in basic experiments, clinical trials have been performed. DeWeese et al (119) performed a phase I clinical trial in which 20 patients with PCa who had relapsed following radiotherapy were treated with CRAd CV706. The clinical results demonstrated a satisfactory treatment effect on PCa without the presence of severe side effects. In addition, Freytag et al (120) constructed an oncolytic virus (ZD55-CD/TKrep) with deletion of E1B-55K and expression of the suicide gene CD/TKrep, which was employed to salvage therapy for 16 patients with PCa who had relapsed following radiotherapy. The clinical results indicated good safety and efficacy. A total of 16 patients were followed for 5 years and the survival rate was 88% (14/16 patients). Furthermore, Freytag et al (121) used an oncolytic virus (ZD55-CD/TKrep) combined with external radiotherapy to treat 15 patients with high-risk PCa. The results demonstrated that the effect of combined therapy was higher compared with radiotherapy alone, however, contradictory clinical effects have also been reported regarding PCa in clinical trials. Small et al (122) conducted a phase I trial of intravenous CG7870 to treat hormone-refractory metastatic PCa. The results indicated a poor treatment effect, and patients with decreased serum PSA levels accounted for only 5/23 patients with PCa. However, no obvious side effects were observed in the 23 patients. Although the majority of clinical trials concerning adenovirus-mediated gene therapy and virotherapy have demonstrated good antitumor effects, biosafety issues arise with adenovirus treatments, particularly tumor-targeting treatments, which limits clinical applications. Consequently, clinical trials involving adenovirus treatments have been stalled in phase I clinical trials. Currently, only one type of oncolytic adenovirus, H101 with deletion of E1B-55K, has been approved for use in patients with advanced tumors, and this approval is only in China.

6. Future directions

Although adenoviruses constructed by different targeting strategies have demonstrated satisfactory targeting effects in the treatment of PCa, each targeting strategy is associated with certain limitations. The combined use of multiple targeting strategies to enhance the adenovirus targeting effect is one promising direction. Currently, several experiments with adenoviruses constructed using multiple targeting strategies have demonstrated that the adenoviruses markedly improve targeting and antitumor effects, including AxdAdB3/RGD (105) with RGD-fiber modification and the EIA/E1B double mutation, Ad53/D24-hNIS (108) with the hybrid Ad5/3 fiber and 24-bp deletion in the E1A-CR2, and DD3-ZD55-SATB1 (114) with the DD3 promoter and EID-55 K deletion, among others. Therefore, the joint use of targeting strategies is an important direction towards enhanced tumor targeting. A list of the adenoviruses constructed using multiple targeting strategies is presented in Table V.
Table IV. Evidence for prostate cancer-targeting strategies of adenoviral mutants.

| Author, year | Therapeutic type | Mutational pattern | Therapeutic genes | Adenovirus | Combination | Experiment type | Result | (Refs.) |
|--------------|------------------|--------------------|-------------------|------------|-------------|----------------|--------|---------|
| Cody et al, 2013 | Virotherapy | A 24-bp deletion in the E1A conserved region 2,Δ24 | OPG | Ad5-Δ24-sOPG-Fc-RGD | NA | In vitro/vivo | Specific inhibition of progression of prostate cancer bone metastases | (102) |
| Hakkarainen et al, 2009 | Virotherapy | A 24-bp deletion in the E1A conserved region 2,Δ24 | NIS | Ad5/3-Δ24-hNIS | Radioiodine therapy | In vitro/vivo | Specific inhibition of prostate cancer cells | (108) |
| Mao et al, 2015 | Virotherapy | Deletion of E1B-55K | shRNA targeting SATB1 | ZD55-SATB1 | NA | In vitro/vivo | Specific inhibition of prostate cancer cells | (114) |
| Ding et al, 2012 | Virotherapy | Deletion of E1B-55K | PTEN | Ad.DD3.D55-PTEN | NA | In vitro/vivo | Specific inhibition of tumor/tumor cell growth | (115) |
| Radhakrishnan et al, 2010 | Virotherapy | Deletion of E3B/a 24-bp deletion in the E1A conserved region 2,Δ24 | NA | Ad-Δ55KA3B | Mitoxantrone/docetaxel | In vitro/vivo | Specific inhibition of androgen-independent prostate cancer/cells | (116) |
| Oberg et al, 2010 | Virotherapy | Deletion of E1B-19K/a 24-bp deletion in the E1A conserved region 2,Δ24 | NA | Ad-ΔCR2Δ19K | Mitoxantrone/docetaxel | In vitro/vivo | Specific inhibition of androgen-independent prostate cancer/cells | (117) |
| Satoh et al, 2007 | Virotherapy | Deletion of E1B-55K/a 24-bp deletion in the E1A conserved region 2,Δ24 | NA | AxDdB-3 | NA | In vitro/vivo | Specific inhibition of androgen-independent prostate cancer/cells | (118) |

OPG, osteoprotegerin; NA, not applicable; NIS, sodium iodide symporter; -55/19K, -55/19 kDa; shRNA, short hairpin RNA; SATB homeobox 1; PTEN, phosphatase and tensin homolog.
Table V. Evidence for the combined use of prostate cancer-targeting strategies.

| Author, year | Therapeutic type | Method of modification of the fiber knob | Mutational pattern | Promoter | Enhancer | Therapeutic genes | Adenovirus | Combination | Experiment type | Result | (Refs.) |
|--------------|------------------|---------------------------------------|-------------------|----------|----------|------------------|------------|-------------|----------------|--------|---------|
| Suzuki et al, 2001 | Virotherapy | Incorporation of an RGD peptide into the HI loop of the fiber knob | A 24-bp deletion in the E1A conserved region 2Δ24 | NA | NA | NA | Ad5-Δ24RGD | NA | In vitro/vivo | Specific inhibition of prostate cancer/cells | (101) |
| Shen et al, 2016 | Virotherapy | Incorporation of an RGD peptide into the HI loop of the fiber knob | SXGXE (STGHE) mutation in E1A/Deletion of E1B-55K | NA | NA | NA | AxdAdB3-F/RGD | NA | In vitro/vivo | Specific inhibition of CAR-deficient prostate cancer/cells | (105) |
| Azab et al, 2014 | Virotherapy | Replacing the Ad.5 fiber knob with the Ad.3 fiber knob | NA | PEG | NA | MDA-7/IL-24 | Ad5/3-PEG-E1A-MDA-7/IL-24, Ad.5/3-CTV | NA | In vitro/vivo | Specific inhibition of advanced prostate cancer/cells | (106) |
| Hakkarainen et al, 2009 | Virotherapy | Replacing the Ad.5 fiber knob with the Ad.3 fiber knob | A 24-bp deletion in the E1A conserved region 2Δ24 | NA | NA | NIS | Ad5/3-Δ24-hNIS | Radioiodine therapy | In vitro/vivo | Specific inhibition of prostate cancer/cells | (108) |
| Hwang et al, 2016 | Virotherapy | Insertion of serotype 35 fiber knob into the serotype 5 backbone | NA | PSES, PSA/PSMA | NA | MDA-7/IL-24 | Ad5/35E1a PSESE4 | NA | In vitro/vivo | Specific inhibition of PSES-positive circulating prostate tumor cells | (112) |
| Ding et al, 2012 | Virotherapy | Deletion of E1B-55K | DD3 | NA | PTEN | Ad.DD3.D55-PTEN | NA | In vitro/vivo | Specific inhibition of tumor/tumor cell growth | (115) |

RGD, arginine-glycine-aspartic acid; NA, not applicable; -55 K, -55 kDa; CAR, Coxackie virus adenovirus receptor; PEG, progression elevated gene; MDA, melanoma differentiation-associated protein; IL, interleukin; NIS, sodium iodide symporter; PSES, prostate-specific enhancing sequences; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; DD3, differential display code 3; PTEN, phosphatase and tensin.
Another promising direction for tumor-targeting strategies takes advantage of the host immune system. The immune system is a potent defensive capability that protects the body from disease, including tumor development and progression. However, certain tumors exhibit host immune tolerance. Adenoviruses armed with cytokines or inhibitors are able to weaken tumor-associated immune checkpoint inhibition, and the host immune tolerance of the tumor may also be reduced (123-125). Following lysis of tumor cells infected by the adenovirus, tumor antigen exposure activates host tumor immunity to induce lysis of metastatic lesions (123). Several adenoviruses have been developed to trigger these oncolytic immunotherapeutic effects, and the results have been satisfactory in certain tumors. Adenovirus mutant Ad5A24/3-RGD-GM-CSF, with expression of granulocyte macrophage-colony-stimulating factor (GM-CSF), exhibits potent antitumor effects in PCa. This construct induced tumor cell death and activated T-cells in response to antigen presentation by exposure of the tumor antigen. The mounted immune response of the injected tumor improved immune recognition to attenuate the growth of distant metastases in PCa (123). Pexa-Vec, which is an oncolytic poxvirus expressing GM-CSF, markedly inhibited tumor progression by inducing host tumor immunity (124). A HSV-1 mutant, termed T-VEC, also expressed GM-CSF to activate antitumor immunity and induced regression of non-injected distal lesions in advanced melanoma (125). Although Pexa-Vec and T-VEC have not yet been used to treat PCa, we hypothesize that treatment of PCa with adenoviruses constructed using an identical strategy may achieve beneficial responses. Adenoviruses armed with cytokines or inhibitors are the most promising strategy for the targeted treatment of early- and late-stage PCa.

7. Conclusion

In conclusion, the tumor-targeting effect is the key point regarding adenovirus-mediated gene therapy and virotherapy. Targeting strategies have been increasingly developed in basic research, however, various limitations remain. Therefore, further research concerning targeting strategies is required to improve the safety of these therapies in the human body and to maximize the net benefit of adenovirus-mediated gene therapy and virotherapy.

Acknowledgements

The present study was supported by the Talent Innovation and Enterprise Program of Lanzhou (grant no. 2015-RC-16).

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