Novel Redirected T–Cell Immunotherapies for Advanced Prostate Cancer

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ABSTRACT

Immunotherapy has failed to achieve durable remissions in advanced prostate cancer patients. More potent T-cell–redirecting strategies may be needed to overcome the immunologically exclusive and suppressive tumor microenvironment. Clinical trials are underway, seeking to define the optimal target for T-cell redirection, such as PSMA, PSCA, or STEAP-1, as well as the optimal strategy, with CAR or bispecific antibodies. As results continue to emerge from these trials, understanding differential toxicity and efficacy of these therapies based on their targets and functional modifications will be key to advancing these promising therapies toward clinical practice. This review provides a unique depth and breadth of perspective regarding the diverse immunotherapy strategies currently under clinical investigation for men with advanced prostate cancer.

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease, causing >30,000 deaths in the United States each year (1). Although many new life- prolonging treatments have been developed over the last decade, all of these eventually fail due to the development of resistance, and durable remissions remain rare beyond first-line therapy. Strategies involving immune-checkpoint inhibitors have been minimally successful (2, 3), and the autologous activated cellular therapy Sipuleucel-T is the only immunotherapeutic that has shown a survival benefit in mCRPC (4). Except for some subgroups yet to be fully defined, mCRPC is regarded as a "cold" tumor characterized by sparse infiltration of lymphocytes and dominance of suppressive immune components including myeloid-derived suppressive cells (5). Thus, additional immunotherapy modalities are needed, and powerful cellular strategies may be key to inducing inflammation in the tumor microenvironment (TME).

Novel immunotherapies that harness the redirection of T lymphocytes against cancer have recently garnered significant attention. In particular, chimeric antigen receptor-modified (CAR) T cells and bispecific antibodies (e.g., bispecific T-cell engagers, referred to as BiTEs), which both utilize single-chain variable fragment (scFv) technologies for the recognition of tumor-associated antigens (TAA), have demonstrated therapeutic promise in hematologic malignancies. Although CAR-T-cell therapies entail an engineered chimeric receptor comprised of an extracellular scFv TAA recognition domain and intracellular CD3ζ and costimulatory domains, BiTE therapies link a TAA scFv with an anti-CD3 scFv, thereby facilitating T-cell–mediated antitumor responses. Importantly, through these novel T-cell redirection approaches, cytolytic T-cell activity may be stimulated in an MHC-independent manner, thus obviating the need for conventional TCR-MHC signaling that may be severely impaired in the "cold" TME of mCRPC.

Both BiTE and CAR-T-cell therapeutic strategies have demonstrated compelling and durable clinical outcomes in a variety of treatment-refractory hematologic malignancies, resulting in several FDA approvals (6–8). More recently, based on this initial success, these T-cell redirection approaches have additionally been applied to the treatment of advanced solid malignancies (9, 10). Both CAR-T-cell and BiTE therapies have been an active area of investigation for the treatment of mCRPC. Indeed, mCRPC offers many potential advantages for the successful development of T-cell–redirecting therapies, including a large unmet clinical need and the availability of a variety of putative TAAs. However, there are several disease-specific aspects of prostate cancer that warrant consideration when developing these therapies. These considerations include the appropriate selection of TAA targets, which vary in their prostate cancer specificity, potential for off- tumor toxicity, functional significance, heterogeneity of expression, and amenability to noninvasive detection. Additionally, the bone-predominant and immune-inhibitory nature of prostate cancer metastases imposes both physical and immunologic barriers to T-cell therapies. Finally, the typical elderly male mCRPC population, often with comorbid medical conditions, may increase the risk for treatment-related toxicities and issues regarding optimal patient selection.

Given the recent high interest in the development and clinical testing of T-cell–redirecting therapies for prostate cancer, this review focuses on BiTE and CAR-T therapies currently under investigation for the treatment of mCRPC. We will specifically discuss current antigen targets, observed barriers to success, and potential future approaches to improve durable remissions for these therapies in mCRPC. In particular, we will review the more well-established cell-surface prostate adenocarcinoma targets, including prostate stem cell antigen (PSCA), prostate-specific membrane antigen (PSMA), and six-transmembrane epithelial antigen of the prostate (STEAP-1), as

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well as implications for future neuroendocrine prostate cancer (NEPC) targets including carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5, also known as CEA) and Notch ligand delta-like protein 3 (DLL3).

Prostate Tumor-Associated Antigens for Redirected T-Cell Therapies

Prostate stem cell antigen (PSCA)

PSCA is a cell-surface glycosylphosphatidylinositol (GPI)-anchored glycoprotein that belongs to the Thy-1/Ly-6 family, which was identified in 1998 as an overexpressed gene in prostate cancer cells and localized to chromosome 8q24 (11). PSCA is expressed in up to 94% of prostate primaries and 87.5% to 100% of prostate cancer metastases with moderate to strong intensity immunohistochemical staining in 84%, weakly positive staining in 17%, and negative staining in 6% (12, 13). PSCA has additionally been noted to be expressed in urothelial, pancreatic, renal cell and non–small cell lung cancers (14, 15) with limited normal tissue expression in the urinary bladder, kidney, skin, esophagus, brain, and stomach (16–18). A summary of PSCA expression is presented in **Table 1**, along with the other prostate cancer TAA that are addressed in this review.

PSCA expression in tumors correlates with disease progression and prognosis in prostate cancer (12, 19–21). For example, PSCA mRNA levels in peripheral blood are also associated with high-grade and extra-prostatic disease (22) and has predictive value for biochemical recurrences and overall survival (23). Therefore, PSCA has been explored as a PET imaging target for cancer detection, staging, and monitoring (24).

The biological function of PSCA is not entirely known; in some studies, PSCA abrogation in cancer cells reduces metastatic potential (25–27), whereas other studies suggest that PSCA suppresses metastasis (28). It is not entirely understood if PSCA is controlled by AR signaling, but studies show androgen-responsive elements in the PSCA gene and the potential for androgen-mediated PSCA expression (29).

Important to immunotherapy considerations, PSCA is immunogenic. PSCA-derived peptides were shown to induce cytotoxic T cells in HLA-A24[+] prostate cancer patients (30). Preclinical studies with PSCA-based vaccines demonstrated long-term protective immunity, without evidence of autoimmunity, in prostate cancer–prone transgenic adenocarcinoma mouse prostate (TRAMP) mice mediated in part by cytotoxic T cells (31). Dendritic cell–based PSCA vaccine approaches yielded similar preclinical antitumor responses (32). A

phase I/II trial recently demonstrated safety and immunogenicity of a prostate cancer–specific self-adjuvanted mRNA vaccine with multiple antigens, including PSCA, further supporting the immunogenicity of PSCA (33).

PSCA can also be targeted using MHC-independent T-cell–engineering therapies due to its cell-surface expression profile. Early attempts of engineered T cells showed *in vitro* targeting of PSCA[+] prostate and pancreatic cancer cell lines using first-generation chimeric antigen receptors (CAR) strategies (34, 35). Hillerdal and colleagues demonstrated antitumor efficacy and prolonged survival of mice bearing subcutaneous PSCA[+] tumors that were treated with third-generation (containing costimulatory domains of CD28 and OX40) PSCA-CAR T cells (36). Superior antitumor activity of CD28 costimulatory domain-containing second-generation PSCA-CAR T cells, compared with third-generation PSCA-CAR T cells, were shown in human xenograft models of pancreatic cancer (17). Subsequent studies further optimized a second-generation CAR-T- cell containing a 4-1BB costimulatory domain for improved tumor selectivity, potent antitumor activity, and bone-homing ability of PSCA-CAR T cells in human xenograft models of bone metastatic prostate cancer (37).

Our more recent study using a fully immunocompetent mouse model of PSCA[+] prostate and pancreatic cancers offered the ability to assess both safety and efficacy of PSCA-CAR T cells. Murad and colleagues demonstrated safety and durable antitumor immune responses with PSCA-CAR T cells (38), even with PSCA expression in various normal tissues including the prostate, bladder, and stomach. Importantly, these preclinical studies also highlight the potential for engaging endogenous immunity in targeting PSCA[+] and PSCA[−] prostate tumors. Two clinical trials of PSCA-targeted CAR-T cells are under way; a summary of ongoing CAR-T and BiTE antibody studies is presented in **Table 2**.

Other T-cell–redirecting approaches have been preclinically evaluated that target PSCA, including bispecific T-cell engagers. CD3-PSCA bispecific antibodies have demonstrated potent and selective CD4^{+} and CD8^{+} cytolytic T-cell activity in cell culture systems (39). Additionally, various formats of novel bispecific antibodies and antibody-based modular targeting of PSCA have shown efficient cell lysis with an ability to further redirect to different TAAs (40). However, bispecific modalities targeting PSCA have not yet been investigated clinically.

Prostate-specific membrane antigen (PSMA)

For nearly three decades, PSMA, a type II transmembrane protein, has been explored as a biomarker of disease activity, as a method for *in vivo* imaging, and as a disease-specific therapeutic target in prostate cancer. The PSMA gene was cloned in 1993 and found to encode a 750-amino acid transmembrane protein (2, 3). The extracellular binding domain of PSMA forms a dimer that binds to glutamate and glutamate-like structures and acts as a glutamate carboxypeptidase. Under normal physiologic conditions, PSMA is found with variable low expression in the prostate gland (secretory acinar epithelium), kidney (proximal tubules), nervous system glia (astrocytes and Schwann cells), salivary glandular cells, and the small intestine (jejunal brush border; ref. 41). However PSMA is highly expressed in malignant prostate tissue and directly correlates with both advancing prostate cancer stage/metastases and higher histologic grade (42). PSMA upregulation may serve as a marker for prostate cancer progression and has been independently associated with prostate-specific antigen (PSA) recurrence following local therapy and with the development of the castration-resistant phenotype (43).

Table 1. TAAs and their expression in type of prostate cancer versus their normal distribution.

Tumor-associated antigen	Cell/tissue distribution
PSCA	**Prostate adenocarcinoma**, urothelial, skin, esophagus, neuronal, stomach
PSMA	**Prostate adenocarcinoma**, prostate acinar epithelium, proximal tubular cells, glial cells, jejunal brush border cells, salivary glandular cells
STEAP-1	**Prostate adenocarcinoma**, bladder, ovary, bone marrow, cardiac, respiratory
DLL3	**Neuroendocrine prostate cancer (NEPC)**, neurons, pancreatic islet cells, pituitary
CEA	**NEPC**, urogenital, respiratory, gastrointestinal

Table 2. List of past, current, and future trials for CAR-T and BiTE therapies in prostate cancer.

NCT#	Biological/drug name	Targets	Status	Phase
CAR-T				
NCT04227275	CART-PSMA-TGFβRDN	PSMA	Active	Phase I
NCT03873805	Autologous anti-PSCA-CAR-4–1BB/TCRzeta-CD19t-expressing T lymphocytes	PSCA	Recruiting	Phase I
NCT04053062	LIGHT-PSMA-CART	PSMA	Recruiting	Phase I
NCT01140373	Engineered autologous T cells	PSMA	Active	Phase I
NCT04249947	P-PSMA-101 CAR-T cells	PSMA	Recruiting	Phase I
NCT04107142	NKG2DL-targeting chimeric antigen receptor–grafted gamma delta T-cell	NKG2DL	Not yet recruiting	
NCT04633148	UniCAR02-T-pPSMA	PSMA	Recruiting	Phase I
NCT02744287	BPX-601	PSCA	Recruiting	Phase I
NCT04429451	4SCAR-PSMA T cells	PSMA	Recruiting	Phase I
BiTE				
NCT04104607	CC-1	PSMA x CD3	Recruiting	Phase I
NCT03406858	HER2 bi-armed activated T cells	HER2 x CD3	Recruiting	Phase II
NCT04702737	AMG 757	DLL3 x CD3	Not yet recruiting	Phase I
NCT03792841	AMG 160	PSMA x CD3	Recruiting	Phase I
NCT02262910	ES414	PSMA x CD3	Completed	Phase I
NCT00635596	MT110	EpCAM x CD3	Completed	Phase I
NCT03927573	GEM3PSCA	PSCA x CD3	Recruiting	Phase I
NCT01723475	BAY2010112	PSMA x CD3	Completed	Phase I
NCT04221542	AMG 509	STEAP-1 x CD3	Recruiting	Phase I
NCT04631601	AMG 160	PSMA x CD3	Not yet recruiting	Phase I
NCT04424641	GEN1044	5T4 x CD3	Recruiting	Phase I/II
NCT03517488	XmAb20717	PDL1 x CTLA4	Recruiting	Phase I
NCT03849469	XmAb22841	CTLA4 x LAG-3	Recruiting	Phase I

Due to its high expression and membrane-bound antigen, PSMA has been proposed as an ideal TAA for targeted prostate cancer therapies. Notably, the expression of PSMA on tumor neovasculature-rich malignancies (ex: renal cell carcinoma and adenoid cystic carcinoma) raise the potential for non–prostate PSMA-directed cancer therapies (44, 45). Although the exact functional significance of PSMA is currently unknown, its extracellular binding domain possesses folate hydrolase activity, and increased PSMA expression may confer a proliferative advantage by increasing the levels of extracellular folate available for prostate cancer cellular import (46). It was recently demonstrated that PSMA interacts with the scaffolding protein receptor for activated C kinase 1 (RACK1), disrupting signaling between the β1 integrin and insulin-like growth factor type 1 receptor (IGF-1R) complex to the mitogen-activated protein kinase (MAPK) pathway, potentiating protein kinase B (AKT) pathway activation instead and thus controlling primary tumor advancement (47). Targeting PSMA-dependent signaling that drives tumor progression may provide a new treatment paradigm due to inhibition of both progression and vascularization, as PSMA blockade with the inhibitor 2-PMPA diminishes integrin activation, endothelial cell adhesion, and angiogenesis (48).

The advent of urea-based small-molecule PSMA ligands has heralded an era of PSMA PET imaging and theranostics. Both ^{68}Ga-labeled (ex: Ga-68 PSMA-11) and ^{18}F-labeled (ex: DCFPyL) PSMA ligands have demonstrated compelling test characteristics for the detection of prostate cancer in men with biochemical recurrence and negative or equivocal conventional imaging, even in patients with low PSA values (49–51). PSMA imaging has paved the way for a theranostic strategy for men with mCRPC—confirming expression of the target antigen radiographically followed by administering a treatment dose radiopharmaceutical. Radiolabeled PSMA ligands (^{177}Lu-PSMA-617) have demonstrated significant antitumor responses, including in cohorts of treatment-refractory mCRPC patients (52, 53). Recently, a large phase III randomized trial demonstrated that ^{177}Lu-PSMA-617 plus standard-of-care treatment improved progression-free and overall survival when compared with standard-of-care treatment alone for men with mCRPC and at least one PSMA PET-avid lesion (54). However, the predictive value of baseline PSMA PET avidity for benefit remains unknown.

A BiTE against PSMA was initially developed in a standard formulation requiring continuous intravenous infusion (AMG212 or pasotuxizumab). A phase I trial (NCT01723475) involving 47 patients showed PSA declines, including two long-term therapeutic responses (55). A reformulation with half-life extension (AMG160) has also been tested in a phase I trial (NCT03792841). This agent yielded PSA50 reductions in 6 of 24 evaluable patients as well as 1 objective radiographic response among 18 patients with measurable disease (56). Two subjects did experience 1 year of cancer control. Toxicity was largely predictable, including cytokine release syndrome in the majority of patients and dry mouth in 28%. Additionally, a PSMA-targeted CAR-T was tested in 5 subjects with mCRPC and evoked PSA declines in 2 men (57). However, the study was stopped due to lack of engraftment. Although sialotoxicity is common with 177Lu-PSMA617 and with AMG160, this has not been reported with PSMA-targeted CAR-T, raising the possibility that on-target off-tumor toxicities may differ between modalities. Ongoing PSMA-targeted immunotherapy trials are summarized in **Table 2**.

Six-transmembrane epithelial antigen of the prostate-1 (STEAP-1)

STEAP-1 is part of the STEAP family that act as ion channels at cell junctions and serve a metalloreductase role (58). Importantly, STEAP-1 has been shown to be overexpressed in prostate cancer as well as in other hematologic and solid tumors. It is expressed in low levels in some normal tissues such as bladder, ovary, marrow, heart, and lung (59). In terms of diagnostic value of STEAP-1, 89Zr-DFO-MSTP2109A is a radiolabeled antibody targeting STEAP-1 that was well tolerated in studies and showed excellent visualization in mCRPC sites including bone and soft tissue, therefore establishing a potential

role as a predictive biomarker for STEAP-1–directed therapy (60). DSTP3086S, a STEAP-1–targeting antibody conjugated with an anti-mitotic agent monomethyl auristatin E, showed some antitumor activity in mCRPC with an acceptable safety profile in a phase I study (61).

For immunotherapy considerations, STEAP-1 is also immunogenic (62, 63). STEAP-1–derived peptides were shown to induce cytotoxic CD8^{+} T cells in an HLA-A*0201–restricted manner, which were shown to be reactive in non–small cell lung cancer and prostate cancer patients *ex vivo* (64).

Vaccine approaches have also demonstrated immunotherapy potential of targeting STEAP-1 (64, 65). As STEAP-1 is primarily expressed at the cell surface, BiTE strategies are also being explored (**Table 2**).

Carcinoembryonic antigen (CEA) and delta-like protein 3 (DLL3)

Although less is known about immunotherapeutic approaches for the treatment of NEPC, recent studies have identified cell-surface targets that may be used to develop CAR-T-cell and BiTE therapy strategies. Most notable has been the identification that human carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5, also known as CEA) is highly expressed in a large subset of NEPC (66). Lee and colleagues recently demonstrated *in vitro* support for the rational targeting of NEPC with CAR-T

cells. In addition, there have been recent promising *in vitro* studies showing successful application of anti-CEA CAR-T cells in CEA-positive solid tumors, further supporting CEA as a potential target for NEPC (67).

Another candidate for immunotherapeutic targeting of NEPC is delta-like protein 3 (DLL3), which was originally identified as an overexpressed surface protein in small cell lung cancer. Recent studies have demonstrated that DLL3 is also highly expressed in NEPC (68) and may also be therapeutically evaluated as both a BiTE (69) and CAR-T-cell strategy for late-stage prostate cancer patients. In fact, DLL3 has been studied extensively as a possible therapeutic target for small cell lung cancer with ongoing phase I trials involving AMG 757 (an anti-DLL3 x CD3 bispecific antibody) and AMG 119 (CAR-T cells directed against DLL3; ref. 69). Although the field is at its infancy in realizing the potential for T-cell–redirecting therapies in treating NEPC, this area of research is likely burgeoning in the coming years, and may provide for an arsenal of cellular immunotherapy approaches in targeting advanced heterogeneous prostate cancers.

Advantages and Disadvantages of T-Cell–Redirected Therapies for mCRPC

A summary of the mechanism of action of BiTE antibodies and CAR-T cells is presented in **Fig. 1**.
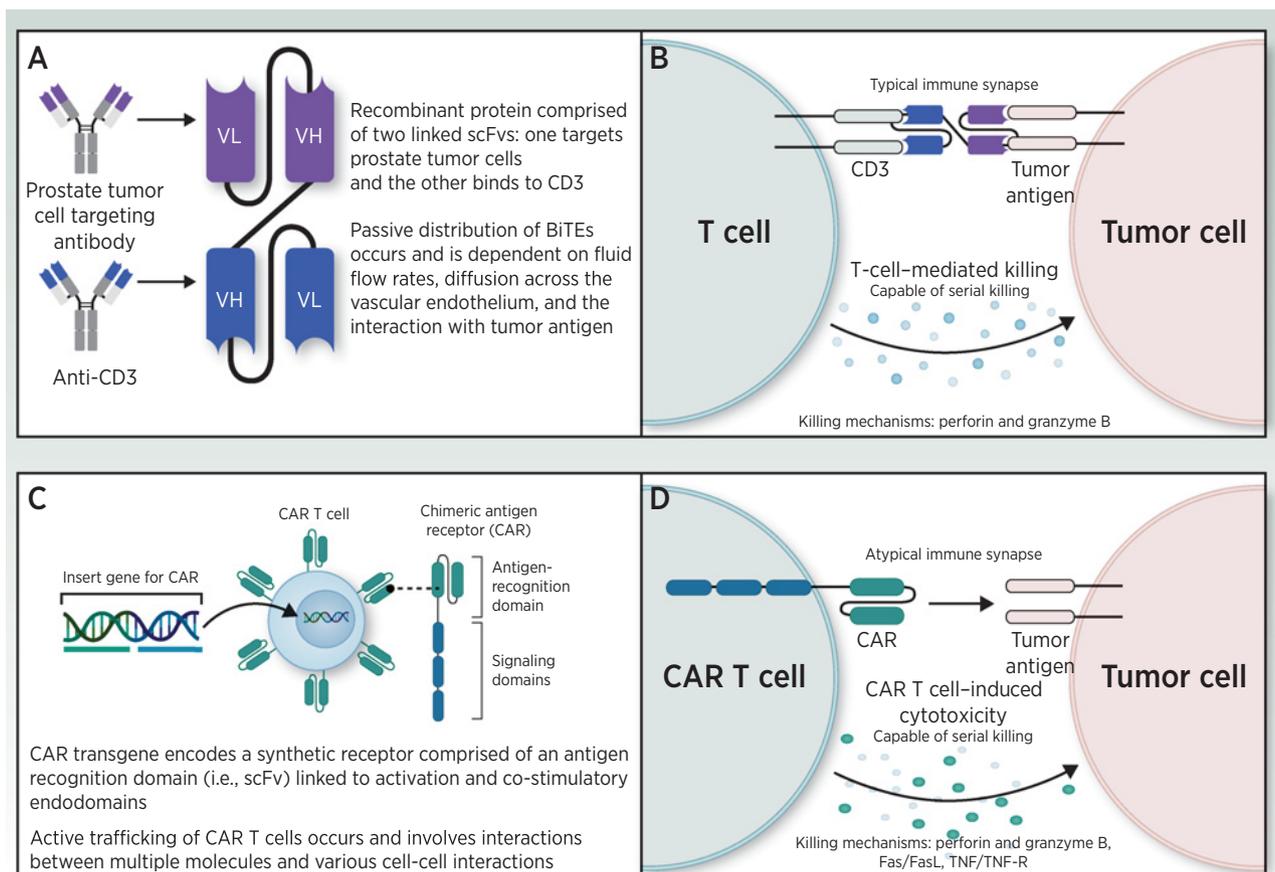

Figure 1.
Mechanisms of action of BiTE antibody (**A**, **B**) and CAR-T (**C**, **D**) therapies.

CAR T-cell therapy in mCRPC

The transformative promise of CAR-T-cell therapy relates to its unique ability to achieve durable clinical remissions for advanced malignancies following a single administration. Indeed, successful *in vivo* expansion of adoptive cell transfer raises the potential for long-term engraftment and antitumor activity (70). Treatment-related factors associated with long-term persistence and clinical remissions in patients with hematologic malignancies treated with CD19-directed CAR-T-cell therapy have included increased peak expansion and immunophenotypic signatures of early memory T-cell differentiation (71). An early stem cell memory differentiation state may offer enhanced cell persistence, and the opportunity for a perpetual source of tumor-reactive T cells though their specificity may be limited by TAA expression heterogeneity. Notably, however, the factors required for the optimal expansion, persistence, and bioactivity in solid tumors, including prostate cancer, remain unknown, and recent solid malignancy experiences have lagged behind those in hematologic cancers, which provide better opportunity for high levels of antigen stimulation and more permissive TME.

One aspect of the prostate cancer TME that may limit CAR-T efficacy is the high level of TGFβ, which inhibits T-cell–mediated immunity. In preclinical studies, the antitumor potency of PSMA CAR-T cells could be augmented by the coexpression of a dominant-negative TGFβRII (TGFβRDN). CAR-T cells engineered to express TGFβRDN (CART-PSMA-TGFBRDN) exhibited increased proliferation, enhanced cytokine secretion, resistance to exhaustion, long-term *in vivo* persistence, and the induction of tumor eradication in aggressive human prostate cancer mouse models (72). In addition, prostate tumor–engrafted mice treated with CART-PSMA-TGFBRDN had significantly higher levels of high-potency central memory CD8+ T cells, compared with mice treated with PSMA CAR-T cells. Although this approach is highly promising, clinical activity has only been observed following infusion of a high number of CART-PSMA-TGFBRDN cells and is tempered by the concomitant induction of cytokine release syndrome, similar to what is observed with CD19-directed CAR-T cells for leukemia. Thus, new strategies are required to improve the persistence of these cells in the toxic TME (**Fig. 2**), while avoiding dose-limiting toxicities.
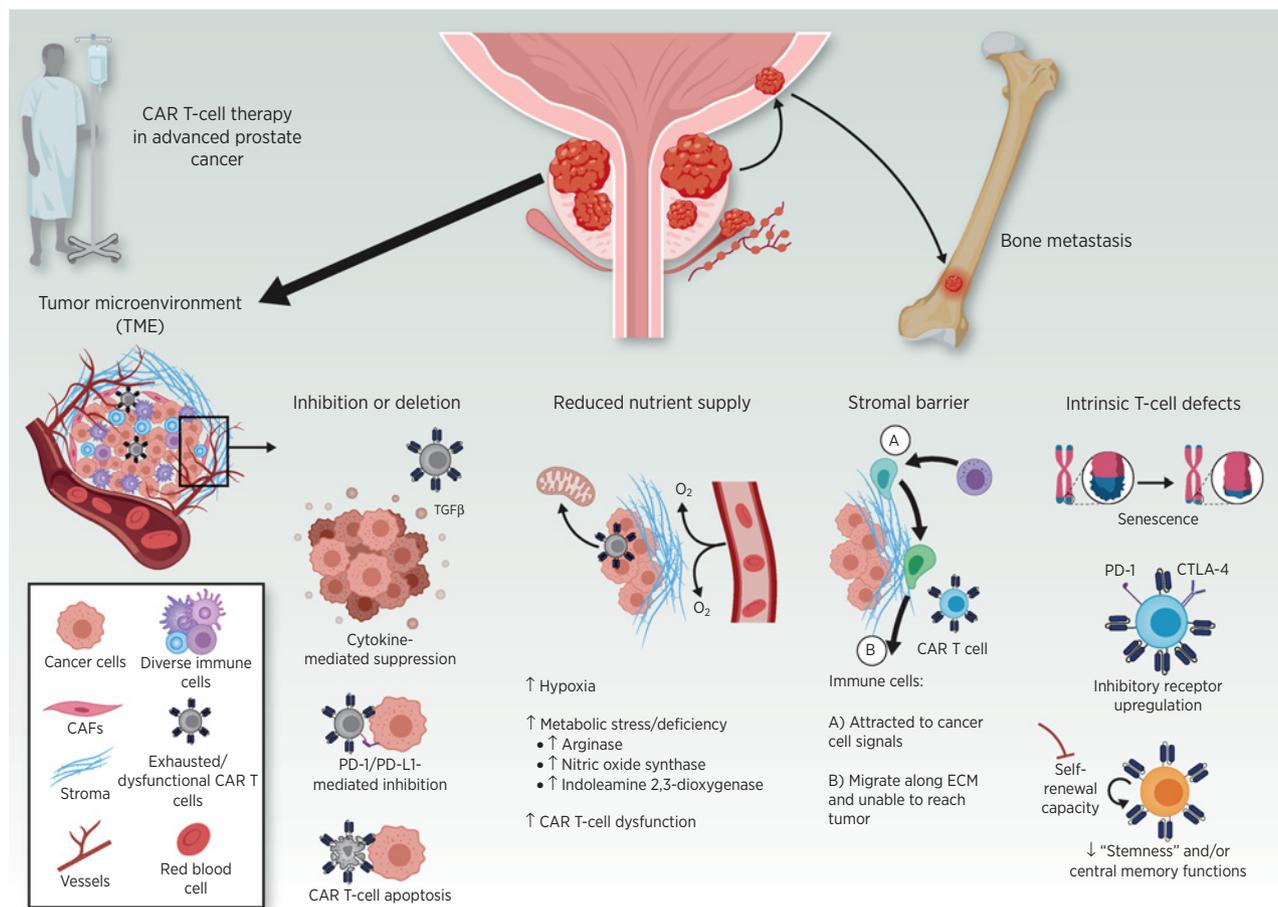

Figure 2.
Immunosuppressive barriers to CAR T-cell function in advanced (metastatic) prostate cancer. Recent studies, including those discussed in this review, suggest that both tumor- and T-cell–intrinsic factors could hamper the efficacy of CAR T cells in prostate cancer. Barriers include elaboration of immunosuppressive cytokines (e.g., TGFβ), increased expression of inhibitory ligands (e.g., PD-L1), apoptosis of CAR T cells, and metabolic stress operative in the TME. A formidable stromal barrier may result in CAR T-cell and bystander immune cell migration along the protumor extracellular matrix (ECM), instead of infiltration into the tumor bed. T cell–intrinsic defects, including replicative senescence, inhibitory receptor upregulation/exhaustion, and reduced early memory T-cell function, may also prevent CAR T cells from eliciting an effective antitumor response.

Even if trafficking and infiltration are successful, T cells can become dysfunctional due to a hostile TME characterized by the presence of soluble inhibitory factors and cytokines, as well as suppressive immune cells or tumor cells that secrete these mediators and overexpress inhibitory ligands. For instance, tumor-infiltrating lymphocytes (TIL) in prostate cancer appear to be defective, in part due to the presence of high levels of arginase, nitric oxide synthase, and indoleamine 2,3-dixoygenase (IDO; refs. 73, 74). IDO inhibitors and other specific combination strategies to overcome the unique TME represent a possible path forward to enhance CAR-T activity in prostate cancer. Even when CD8$^+$ T cells are effective in mediating tumor cell lysis, the localization of cytotoxic T lymphocytes (CTL) within prostate tumors is modest relative to the infiltration of these tumors with myeloid-derived cells (75). The immunosuppressive TME formed by myeloid-derived cells (PMN-MDSC/neutrophils, TAMs, mMDSCs, and suppressive dendritic cells) hampers antitumor immunity and effective treatment in prostate cancer, and this is supported by clinical evidence (76). T-cell–intrinsic defects, such as upregulation of inhibitory receptors (e.g., PD-1 and CTLA-4), a reduction in "stemness"/self-renewal capacity, as well as impaired central memory functions, increased apoptosis sensitivity and augmented replicative senescence are also major barriers to the success of CAR-T cell therapy (77, 78). Accordingly, checkpoint blockade therapy combined with targeted agents that inhibit MDSCs without impacting T-cell function results in robust immunotherapy of mCRPC (79). Another issue of the hostile TME is the accumulation of prostate cell secretion products that can be inhibitor to T cells. In particular, the polyamine spermine has been shown to have immunosuppressive effects on T cells including downregulation of cytokine secretion and decreased cytotoxic activity (80, 81).

It has recently been shown that conditioning chemotherapy, commonly referred to as "lymphodepletion," plays a critical role in modulating the TME for CAR-T cell effect. In particular, cyclophosphamide administration increased intratumoral PSCA-targeted CAR-T cell accumulation and expansion *in vivo* (38). Gene ontology enrichment analysis identified T-cell migration and IFNγ production as key processes enhanced by cyclophosphamide pretreatment. In addition, Alzubi and colleagues showed significant inhibition of tumor growth in prostate cancer xenograft models when they were treated with PSMA-targeted CAR-T cells in combination with low-dose docetaxel, compared with each component individually (82). Further work will elucidate which immunosuppressive components these chemotherapy regimens help to overcome, which will inform exploration of additional strategies to modulate TME for enhanced success with cellular immunotherapy. However, conditioning chemotherapy regimens are not without their own side effects including myelosuppression, leading to potentially life-threatening infections (83). Study of CAR-T cells alone, without conditioning chemotherapy, and vigilance toward the contribution of chemotherapy to the overall toxicity of the treatment will be keys to maximizing patient safety.

Finally, important practical and toxicity considerations must be addressed during the development of CAR-T therapies in advanced prostate cancer. The collection, manufacture, release testing, and administration of autologous CAR-T therapies pose limitations to patient selection in prostate cancer, particularly when heavily pretreated patients may develop rapid disease progression. In addition, the unpredictable and potentially severe treatment-related toxicities associated with CAR-T therapy (84) raise concerns in an elderly prostate cancer population. Similar to the experience with anti-CD19 and other CAR-T therapies for hematologic malignancies, the solid tumor experience to date has reported high-grade cytokine release syndrome (CRS), neurotoxicity (ICANS), on-target/off-tumor effects, and severe allergic reactions (85, 86). Moreover, in the mCRPC experience to date, the reported time course for onset of high-grade CRS, neurotoxicity, and other severe inflammatory events has varied (within 6 hours of infusion to several weeks after infusion), which may limit the ability to reduce inpatient and outpatient observation period (87). Additionally macrophage activation syndrome has been a serious toxicity in prostate cancer CAR-T trials (86), but can be abrogated, indicating a need for highly specialized treatment teams in order to optimize patient safety, especially during early-phase trials. Moving forward, the development of predictive models for CAR-T–related CRS and other toxicities, using disease-related variables and early cytokine inputs, may provide needed guidance for prostate cancer–specific CAR-T toxicity identification and management.

BiTE therapy

Bispecific antibody therapies, including BiTEs, have seen an explosion of clinical development over the past several years (88). A major advantage of BiTE therapy is the fact that it is not an individually produced cellular product, making it easier to scale for widespread use (89). Another advantage perhaps is the different tumor penetrating capabilities of antibody therapies as compared with cellular therapies. It is likely that BiTEs arrive at the tumor site either through direct biodistribution to tumors or through "backpacking" via TILs. BiTE therapies also differentiate from CAR-T cells in the kinetics and severity of CRS, which have been relatively predictable and manageable with mitigation strategies and may result in less need for ICU-level care or tocilizumab administration (90).

A major disadvantage of BiTE antibody therapy is that, in its more common format, it requires repeated dosing either weekly or bimonthly, though this is feasible and preferable to continuous infusion. Although toxicity is predictable, the frequency and severity of CRS seen with AMG160, for instance, necessitated dexamethasone premedication for the first several doses (56). There is concern that steroids may blunt the full potential of a T-cell–mediated antitumor response (91). Furthermore, efficacy has been correlated to the level of TILs, and therefore success may require an already immunologically "warm" tumor. And finally, BiTE antibodies may also generate anti-drug antibodies; the extent to which this occurs and how much this limits efficacy remains to be determined (56).

Future Directions

Based on our early experiences, it is likely that combination therapies will be needed to induce significant and durable remissions with solid tumor T-cell–redirected therapies. These combination strategies will require identification of resistance mechanisms, ideally from patient blood and biopsy samples, though preclinical models may be helpful in preliminary mechanistic studies. For instance, adding immune-checkpoint inhibitors would be considered if there is evidence of T-cell exhaustion in patient samples after exposure to a T-cell–redirected therapy, whereas something to reverse the immunosuppressive TME and promote tumor infiltration of T cells in advance of CAR-T-cell or BiTE therapy may be required if inadequate trafficking of T cells into the tumor is identified. Additionally, structural modifications to circumvent stromal barriers may be needed to enhance antitumor activity of CAR-T cell therapies. For example, CAR-T cells redirected toward fibroblast activation protein-α, which is highly expressed on cancer-associated fibroblasts, demonstrated target cell lysis and therapeutic synergy with TAA-redirected CAR-T cells for solid tumors (92). Additionally, CAR-T cells engineered to express

heparanase, which is involved in the degradation of heparan sulfate proteoglycans within the extracellular matrix, aided TILs and antitumor activity (93).

Additionally, heterogeneity of neoantigen expression or dedifferentiation is often seen in late-stage or heavily pretreated mCRPC. Epigenetic studies have identified differences in tumor RNA splicing among men of differing ethnic backgrounds (94), which may lead to racially described differences in neoantigen expression and outcomes, but it is likely that specific molecular diagnostics to characterize an individual's expression of the target antigen will be needed to enrich clinical trials to maximize benefit. Multitargeting approaches may also be required to account for tumor antigen heterogeneity; future strategies include next-generation CAR-T cells designed to target two or more antigens simultaneously (i.e., tandem scFvs on CARs, multiple BiTE coinfusions), or BiTE-secreting CAR-T cells (95). There is also increased NEPC after the application of more potent antiandrogen therapies. This has been noted incidentally on some on-study and posttreatment biopsy samples in our experience, which makes dual targeting of traditional plus neuroendocrine antigens attractive.

As discussed extensively in this review, novel immune therapies provide a promising new avenue of treatment for advanced prostate cancer with the possibility of sustained, durable responses. Further modifications to CAR-T cells, or the addition of adjunctive therapies, may be needed to overcome the immune-suppressive microenvironment and physical barriers unique to prostate cancer. Although preclinical models can reveal potential BiTE and CAR-T-cell potency-enhancing or toxicity-mitigating strategies in the presence of a target antigen-expressing tumor, we acknowledge that there are many limitations of preclinical models, and these findings therefore may not translate fully into improved activity during future clinical applications. Well-defined toxicity management protocols will be crucial in order for these treatments to be offered more broadly. Certification or at least robust training will be needed to maintain safety of these therapies and even regionalization to specialized center may end up being necessary to ensure their proper use. Despite all of this, we are optimistic that these therapies may become a significant therapeutic advance in the future.

Authors' Disclosures

Acknowledgments

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