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Prostate cancer surface targets for CAR T cell therapy or metastatic prostate cancer in the CAR T cell era: My kingdom for the target!

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Summary

Despite the progress achieved in target, chemo-, and radiotherapy, treatment options for patients with late-stage metastatic castration-resistant prostate cancer are presently very limited. Use of dendritic cell-based vaccines exemplified by sipuleucel-T appears is rarely curative and is effective in only a fraction of such patients. Given the success of CAR T cell therapy in the field of B cell malignancies, significant efforts have been made to adapt this powerful technology to the problem of metastatic prostate cancer. Availability of unique prostate cancer surface targets for CAR T cells has thereby become a pressing issue in the field of CAR design. Ideally, such targets should be absent from normal cells or tissues, be present on all prostate cancer cells across all patients, and be indispensable for the survival of cancer cells. In reality, however, none of the prostate cancer-associated surface markers described to date are matching such description. Here, we catalogue the list of tested as well as prospective surface antigens to be used as targets for CAR T cell therapy, and discuss the aspects of their safety and potential efficacy.

Keywords

Metastatic prostate cancer, immunotherapy, chimeric antigen receptor, CAR T cells.

Introduction

Treatment of cancer via adoptive transfer of CAR T cells, being proposed over 20 years ago, remained essentially unknown to the broad medical community, largely due to its very limited efficacy observed in clinical trials. CAR T cell-based therapy came into spotlight when complete responses, many of which were long-lasting, had been reported for 50-90% patients with refractory/relapsed acute lymphoblastic leukemia (r/rALL) and B-cell lymphomas [1-7]. This success stemmed from the relatively easy access of CAR T cells to cancer cells, as well as from the broad choice of targetable surface markers present on the surface of malignant B cells. In the case of ALL, these markers include pan-B cell antigens such as CD19, CD20, CD22, etc. Accordingly, normal B cells expressing the same surface markers may also be destroyed by CAR T cells [2, 3, 5]. However, this so-called "on-target off-tumor" activity is well tolerated and can be compensated by immunoglobulin replacement therapy [8]. This may not be the case, however, for most other malignancies, since cancer cells often express surface markers that are shared with normal tissues vital to the patient. Thus, the availability of a specific surface marker is central for any successful anti-cancer CAR T cell therapy, including that for prostate cancer (PCa).

Selecting a CAR target

An ideal target for CAR-based PCa therapy should display the following features: i) strong and homogeneous expression on metastatic PCa cells and limited or absent expression on non-malignant cells, ii) it should be indispensable for the growth of PCa cells, and/or iii) be enriched on the PCa stem cell population. Comprehensive and unbiased profiling of metastatic PCa-specific surfaceome is therefore warranted as this information would be instrumental for the design of highly selective and potent CARs for the therapy of PCa.

Below we summarize the data on the surface antigens having limited expression outside the prostate and PCa lesions. These targets were used for the preclinical and/or clinical development of CAR T cell-based approaches for PCa or are expected to become CAR T cell targets in the nearest future.

PSCA is a small highly glycosylated GPI-anchored protein with apparent molecular weight of ~24 kDa and predicted molecular weight of only ~10 kDa. First described in 1998, this protein has immediately attracted attention as a potential target for anticancer therapy: it was shown to be highly expressed in primary tumors and metastases of over 80% PCa patients [9-11], as well as in up to 60% pancreatic [12, 13] and bladder [14] cancer samples. It should be noted however, that PSCA expression is not restricted to the malignant prostate cells. By profiling human tissues using a PSCA-specific monoclonal antibody 1G8, various levels of PSCA expression were found for normal epithelial (basal, secretory, and neuroendocrine) cells of the prostate, transitional epithelium of the bladder, neuroendocrine cells of the stomach and the colon, as well as for collecting ducts of the kidney [10]. A number of PSCA-specific monoclonal antibodies and humanized variants thereof have been extensively characterized pre-clinically [15, 16], however they never proceeded to advanced clinical stages as monotherapy agents. Notably, 1G8-based PSCA-specific CAR T cells were shown to significantly inhibit growth of PSCA-positive non-small cell lung cancer patient-derived xenografts in mice, which provided the rationale for moving towards a clinical trial of CAR T cells in lung cancer patients (NCT03198052). Furthermore, a "switchable" PSCA-specific GoCAR T cell product (BPX-601, Bellicum Pharmaceuticals) is currently in a Phase1/2 clinical trial for patients with PSCA-positive gastric, pancreatic, and prostate tumors (NCT02744287). Whereas the data for prostate cancer patients are pending, recent analysis of several small cohorts of heavily pre-treated pancreatic patients indicates that BPX-601 infusion combined with a single injection of the small-molecule "switch" has resulted in disease stabilization, which was accompanied by generally moderate and reversible toxicities [17].

Prostate-Specific Membrane Antigen (PSMA) is a type II 100 kDa transmembrane glycoprotein frequently found in both PCa tumors in addition to a limited number of normal human tissues such as prostate epithelium, proximal renal tubules, duodenal, and rectal mucosa [18, 19]. Interestingly, in the LNCaP cell line widely used for PCa research, PSMA expression is partially modulated by steroid hormones [18]. This recapitulates the *in vivo* situation, as PSMA expression has been reported to be up-regulated in primary PCa tumors and metastases following androgen-deprivation therapy [20]. Nonetheless, different research groups reported the percentage of PSMA-positive prostate tumors to vary from 66 to 100% [19, 21, 22], which is likely attributable to the choice of the PSMA-specific antibody. Interestingly, PSMA is known to mark the neovasculature of various non-prostatic cancers [19, 23]. Several small-molecule inhibitors with high affinity to PSMA and PSMA-specific antibody-drug conjugates have been characterized and are now actively tested for imaging purposes (reviewed in [24]) or as therapeutic agents in Phase 2/3 clinical trials (NCT03042312; NCT02615067; NCT03511664). Excellent safety profile of such PSMA-targeted molecules establishes PSMA as a strong target for CAR T cells in the context of both metastatic PCa lesions and neovasculature of cancers other than PCa (NCT00664196, NCT01140373, NCT03089203).

ErbB2 (Her2/Neu) is a transmembrane protein known as a prominent marker of breast and gastric carcinomas. Low-level ErbB2 overexpression was found in ~20% of PCa tumors, with stronger expression correlating with rapid cancer cell proliferation and tumor recurrence [25]. Multiple ErbB2 ligands currently approved as therapeutics (such as trastuzumab and pertuzumab) make this protein a convenient target for adoptive cellular immunotherapy of PCa. Although infusion of a ErbB2-specific CAR T cell product has been implicated in a death of a clinical trial participant [26], the reason behind such outcome was likely unrelated to "on-target off-tumor" activity which would be consistent with the broad low-level expression of ErbB2 on normal epithelial cells [27], as this was not observed in a later study where a distinct anti-ErbB2 CAR and significantly lower CAR T cell dose were used [28, 29].

EpCAM (CD326) is frequently found on the surface of carcinomas of various origin, including the prostate, where this antigen was reported to be expressed in up to 87% of tumors [30]. This protein is also considered to be a cancer stem cell marker [31], which strengthens the idea of its use as a therapeutic target. Yet, EpCAM is also expressed at the basolateral cell membrane of simple, pseudo-stratified, and transitional epithelia, which raises reasonable safety concerns for EpCAM-specific CAR T cell therapy. Presently, EpCAM-specific CAR T cells are in Phase 1/ 2 clinical trials for several solid cancers (NCT02729493, NCT02725125, NCT03563326, NCT02915445) including PCa (NCT03013712).

CD133 (Prominin-1) is one of the several controversial markers of cancer stem cells known to be also expressed by normal stem cells and terminally differentiated epithelial cells [32]. In fact, in the context of PCa, CD133 labels only a subset of cancer stem cells [33,34], which may limit the clinical relevance of this protein as a sole CAR target. It must be noted that a recent clinical trial of CD133-specific CAR T cells for the therapy of patients with hepatocellular, pancreatic, and colorectal carcinomas suggested their overall safety and evidence of limited efficacy [35]. This was consistent with a modest pre-clinical *in vitro* and *in vivo* activity of these CAR T cells. Not a single complete response was observed among the 23 treated patients most of whom had very bulky lesions and could not be pre-conditioned. Importantly, CD133+ cells were depleted from the tumor bioptates

post-treatment and a CD133- tumor escape was observed in one patient. This finding indicates that a two-pronged approach of simultaneously attacking the cancer stem cell population and the tumor cell mass should translate into stronger responses. Therefore, CAR T cells designed to target both CD133 and the surface markers of more differentiated cancer cell types, such as CD133+CEACAM5 or CD133+EGFR, should be more actively explored both pre-clinically and in the clinical setting [36]. So far, no studies of CD133-specific CAR T cells for the therapy of PCa patients have been reported.

Yet another marker of both cancer and hematopoietic stem cells, **CD44**, is known to be expressed by PCa stem cells [37]. Interestingly, a variant splice form of CD44 known as **CD44v6** is not expressed by hematopoietic progenitor cells, and is considered as a favorable target for CAR T cell therapy [38]. CD44v6-retargeted CAR T cells have shown impressive pre-clinical activity in several hematological cancer models [38,39], but none have so far been specifically evaluated in the context of PCa.

PCTA-1 (Galectin 8) was described as the protein expressed on PCa cells back in 1996 [40], however later it received very little attention as a therapeutic target. Likely this was due to the fact that it was and still is unclear how this protein devoid of the signal sequence is trafficked outside the cell and ultimately reaches the cell surface [41-43] and whether its surface expression is truly restricted to cancer cells (reviewed in [44, 45]). It has recently been demonstrated that patients with metastatic castration-resistant prostate cancer who received Sipuleucel-T produced significantly higher titers of PCTA-1 specific antibodies compared to the control group of patients [46]. This and other observations [47] highlight PCTA-1 as an emerging therapeutic target in PCa.

STEAP1 has been identified as a membrane protein that is overexpressed in metastatic PCa lesions compared to benign prostatic hyperplasia [48]. It was shown to be also expressed, albeit at much lower levels, by normal prostate and urinary bladder cells, however current expression profiling data are indicative of a much broader normal tissue expression of STEAP1 which includes the brain and the lungs [49]. Whether this inconsistency is associated with the specific choice of antibodies used remains to be explored. Nonetheless, recent clinical trial of MSTP2109A, a conjugate of a humanized anti-STEAP1 antibody and MMAE, has provided evidence of its moderate efficacy in the therapy of patients with metastatic castration-resistant prostate cancer (mCRPC), which was accompanied with a significant percentage of treatment-related serious adverse events [50]. Therefore, considering STEAP-1 as a possible target for CAR T cells may not be regarded as straightforward.

Survivin is broadly known as an intracellular anti-apoptotic protein involved in the control of cell proliferation [51]. It is up-regulated in multiple human cancers including PCa [52]. Intriguingly, this protein has recently been shown to be present on the surface of cancer cells [53], thereby lending itself as a prime candidate for Survivin-specific CARs.

MUC1 is expressed by tumors of a fraction of PCa patients. Across different studies, the percentage of MUC1-positive tumors ranges from 17% [54] to 58% [55]. Notably, MUC1 is also expressed by various types of epithelial cells, as well as by hematopoietic cells and activated T cells [56]. This broad expression pattern across multiple normal cell types sets MUC1 as an antigen that appears suboptimal for the target therapy of PCa. Nonetheless, recent efforts from two companies, Minerva Biotechnologies and Poseida Therapeutics, to identify binders that can reliably discriminate between cancer-specific MUC1 species (known as MUC1* or MUC1C) and the full-length MUC1 present on normal cells, have translated into the design of CAR T cells [57] showing robust anti-tumor activity in mouse xenotransplant models [58-60], with a Phase I clinical trial of MUC1*-specific CAR T cells announced for breast cancer patients (NCT04020575).

At the same time, **Tn Muc1/sTn Muc1** species predominantly, although not exclusively expressed on the surface of cancerous, rather than normal tissues serve as attractive alternatives to MUC1 for CAR T cell-based therapy [61, 62], with a recently opened early phase clinical trial of TnMuc1-specific CAR T cells in advanced (non-PCa) solid cancer and multiple myeloma patients (NCT04025216). Except for one report [63], expression of these glycopeptide antigens has been extensively explored using a number of mAbs [64-66] (reviewed in [67]) in cancers other than PCa [61,68]) and warrants further investigation, as the data have been somewhat difficult to reconcile [69].

TAG-72 epitope, established to be a sialyl-Tn O-glycan carbohydrate hapten, has been found in the vast majority of human carcinomas, including PCa. Given its rather restricted expression pattern in normal tissues [70,71] and favorable safety profile of anti-TAG72 mAbs [72,73], first-generation TAG-72-specific CAR T cells have been extensively evaluated both pre-clinically [74] and in two early clinical trials [75] for metastatic colorectal cancer, where they proved to be safe and inefficient largely due to the poor persistence afforded by the CAR design and rapid anti-idiotype elimination. Recent study using local delivery of optimized second-generation TAG-72-CART cells in a xenotransplanted ovarian cancer model [76] provides a strong rationale for testing TAG-72 as a promising target for CAR T cells in epithelial carcinomas including PCa.

Integrin αvβ3 is another marker frequently found on PCa cells, as well as on endothelial cells of the tumor vasculature. Expression of this protein is associated with higher risk of metastatic bone lesions [77-79]. Monoclonal αvβ3-specific antibody LM609 and a humanized derivative of LM609 have been characterized in phase I clinical trials which confirmed their safety [80], however no reports of therapeutic activity in the completed phase II clinical trial (NCT00072930) have been posted since 2008, consistent with the complex biology of αvβ3 in cancer [81]. Intriguingly, a recent study reported on the activity of hLM609-derived αvβ3-specific CAR T cells both in vitro and in vivo, in the setting of xenotransplanted human melanoma [82].

CEACAM5 and **CEACAM6** are two related proteins expressed at comparable levels on both PCa and normal prostate cells [83]. Variable levels of expression of these proteins have also been reported for normal cells of the lung, pancreas, and intestine. Safety of the cell therapy targeting

CEACAM5 was analyzed in several studies and the results were somewhat conflicting. Use of CEACAM5-specific recTCR-T cells was accompanied with serious colitis in all three patients who received the cell products [84]. This was unlike the situation reported for CEACAM5-specific CAR T cells based on the MFE23 scFv, where acute respiratory toxicity was observed [85]. Notably, infusion of CEACAM5-specific CAR T cells based on the alternative antigen recognition modules was not accompanied with critical adverse effects in two more clinical studies [86,87]. So far, CEACAM5-specific CAR T cells have not been tested in PCa patients. As for, CEACAM6-specific CAR T cells, the studies have not yet progressed beyond mouse xenotranplant models, and safety of such CAR T cells in humans is presently unknown [88].

TROP-2 (TACSTD2) is expressed on both benign and malignant prostate lesions [89, 90], yet it is also detectable on the normal epithelial cells of various origin [91]. No clinical trials of TROP-2-specific CAR T cells have so far been approved, however TROP-2-specific antibody-drug conjugates have been tested in patients and numerous adverse effects have been reported [92]. Hence, the safety of TROP-2-targeted CAR T cell therapy is presently questionable.

Finally, two B7-CD28 family members, **B7-H3 (CD276)** and **B7x (VTCN1/B7-H4)** have been reported to be overexpressed in a variety of cancers including PCa [93,94] (reviewed in [95,96]), and are currently the focus of pre-clinical CAR T cell evaluation programs using AML [97], lung [98], breast [99], bile duct [100], bone and brain [101-103] cancer cells as the targets. Importantly, the findings of Phase I/IIa clinical trials of B7-H3-specific monoclonal antibody MGA271 (enoblituzumab) support its favorable safety profile [104], although surface expression of B7-H3 has been demonstrated for several normal cell types such as dendritic cells, as well as *in vitro* activated T-, NK- and B cells [105]. Accordingly, B7-H3-specific CARs did not display appreciable off-tumor activity in pre-clinical tests, but they may still require structural/affinity optimization to robustly discriminate between different expression levels of this antigen on normal and malignant cells upon transition to human trials. Interestingly, delayed lethal off-tumor toxicity has recently been observed for B7x-specific CAR T cells [106].

Conclusion

None of the abovementioned markers are absolutely specific for PCa or found across PCa lesions in all patients. Furthermore, a fraction of PCa tumors may be expected to be negative for all such markers, and, hence, the feasibility of delivering a targeted CAR therapy would be very low in such cases. Thus, systematic discovery of novel PCa surface markers is highly warranted. Only a handful of studies in this direction have been published to date. For instance, using a combination of proteomic and transcriptomic profiling, Lee and colleagues have identified a number of surface markers enriched in PCa subtypes [107]. Whereas the identification of known PCa markers such as CEACAM5, PSMA, STEAP1, MUC1, and TROP-2 clearly validates this approach, the rest of the high-ranking proteins reported appear to be strongly and broadly expressed in essential tissues, which makes unlikely their potential use as CAR targets.

Analysis of antibodies present in the sera of convalescent cancer patients following immunotherapy who have developed an anticancer immune response may represent an interesting resource of antigen-recognition modules in CAR design. In line with this idea, GuhaThakurta and colleagues have profiled the specificity of antibodies from 25 mCRPC patients who received a dendritic cell-based vaccine sipuleucel-T [46]. Moderate, yet significant increase in antibody titers to PCTA-1 and Galectin-3 among others was observed. The former protein has already been known as a PCa marker, whereas the latter is predominantly secreted, and is a poor candidate for CAR targeting. Nonetheless, in our opinion this approach appears highly promising. In the context of other types of cancer, antibody profiling has identified a number of putative cancer markers including Galectin-1 [108], MYPT1, PSMC5, etc [109]. Importantly, despite the fact that the above proteins lack protein domains that would anchor them at the cell surface, this approach may still be fruitful once substantially more patient samples are analyzed. Of special interest is the recent advance in the technology of single-cell profiling of repertoires of B- and T- cell receptors [110], which may help identify target-receptor pairs, once combined with the proteomics data. Using the above approaches, analysis of samples from more PCa patients may be required to capture novel or subtype-specific PCa markers, or to confidently conclude that no such targets beyond the described ones exist, and that combinations of the known targets should be exploited for CAR design.

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Метастатический рак простаты в эпоху CAR T-клеточной терапии: «Полцарства за мишень!»

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Резюме

Несмотря на значительный прогресс в области таргетной, химио- и радиотерапии, количество вариантов для пациентов с метастатическим кастрационно-резистентным раком предстательной железы остается невысоким. Большие надежды возлагались на дендритно-клеточные вакцины, в частности на sipuleucel-T, однако не все пациенты отвечают на этот тип терапии. Учитывая впечатляющий успех CAR T-клеток для лечения онкогематологических заболеваний, многие исследовательские группы начали разработку подходов CAR T-клеточной терапии кастрационно-резистентного рака предстательной железы. Из-за этого особенно актуальным стал вопрос об уникальных белках-мишенях рака простаты для CAR T-клеточной терапии. В идеале такие белки должны отсутствовать на поверхности нормальных клеток, экспрессироваться на всех раковых клетках у всех пациентов и быть незаменимыми для выживания раковой клетки. На практике, однако, ни один из описанных к настоящему моменту поверхностных белков-маркеров рака простаты не отвечает всем указанным требованиям. В настоящем обзоре рассмотрены основные белки-мишени для CAR T-клеточной терапии рака простаты, обсуждается их безопасность и потенциальная эффективность.

Ключевые слова

Метастатический рак предстательной железы, иммунотерапия, химерные антигенные рецепторы, CAR T-клетки.