SCANDINAVIAN JOURNAL OF UROLOGY
2022, VOL. 56, NO. 2, 126–130
https://doi.org/10.1080/21681805.2022.2049362

ARTICLE

The role of single-nucleotide polymorphisms of the 8q24 chromosome region in patients with concomitant bladder and prostate cancer

Georgios Gakis[a], Sven Perner[b,c], Arnulf Stenzl[d] and Markus Renninger[d]

[a]Department of Urology and Pediatric Urology, University Hospital of Würzburg, Julius-Maximillians University, Würzburg, Germany; [b]Institute of Pathology, University of Luebeck, University Hospital Schleswig-Holstein, Campus Luebeck, Luebeck, Germany; [c]Department of Pathology, Research Center Borstel, Leibniz Lung Center, Borstel, Germany; [d]Department of Urology, University Hospital, Eberhard-Karls University, Tübingen, Germany

ABSTRACT

Objective: To assess whether single-nucleotide polymorphisms (SNPs) of the 8q24 chromosome region are associated with recurrence-free survival (RFS) after radical cystoprostatectomy (RC) in patients with concomitant bladder (BC) and prostate cancer (PC).

Materials and methods: A cohort of thirty-six patients treated with RC and pelvic lymph node dissection and histologically exhibited invasive BC and incidental PC. Using Sanger sequencing, a total of seven SNPs in the androgen-responsive element of the promoter region of the following genes were assessed in tumor-free lymph nodes and correlated with oncological outcomes: PSCA (rs2294008, rs2978974, rs1045531, rs3736001), MYC (rs6983267), FXBO32 (rs7830622), and MIR151A (rs14974929). The median follow-up was 26 months (range: 4–68).

Results: In a dominant model, patients exhibiting rs2978974 as a minor allelic variant of the PSCA gene had worse RFS (32 *vs.* 75%, $p = 0.015$). No associations were found for the other SNPs.

Conclusions: These data suggest that the rs2978974 of the PSCA gene correlates with inferior BC-specific RFS after RC and should be further evaluated in larger studies.

ARTICLE HISTORY
Received 31 December 2021
Revised 23 February 2022
Accepted 26 February 2022

KEYWORDS
Bladder cancer; PSCA; radical cystectomy; recurrence; rs2978974; SNP

1. Introduction

Based on the observation of a higher incidence of bladder cancer (BC) in men than in women and a high rate of incidental prostate cancer (PC) during radical cystoprostatectomy (RC), it can be hypothesized that sex steroids may play a role in the development and progression of BC [1,2]. Results from the prospective Prostate-Lung-Colorectal-Ovarian (PLCO) study demonstrate that a variety of single-nucleotide polymorphisms (SNPs) on chromosome 8q24 correlate with increased serum concentrations of androgens, dihydrotestosterone (DHT), and sex-hormone binding globulin [3]. Thus, the question arises whether SNPs from this chromosomal region could corroborate the theory of sex steroid-based progression of BC at the predisposing level. Indeed, SNPs on chromosome 8q24 were found to be associated with an increased risk of developing PC or BC [4–7]. The prostate stem cell antigen (PSCA) gene is located on chromosome 8q24.3 and has an androgen-responsive element in its promoter region [8]. Recent data suggest that the SNP rs2978974 is located in an androgen-responsive element of the PSCA gene [7]. Recent genome-wide association studies (GWAS) on BC demonstrate that the SNPs rs2294008 and rs2978974 are associated with an increased susceptibility risk for BC [5,7]. rs2294008 was also investigated in a genotyping of 12 SNPs of the PSCA gene in 194 PC patients and 167 healthy controls. It was found that individuals with haplotypes rs2294008, rs3736001, and rs1045531 had a significantly increased risk of developing PC [9]. In another GWAS, the SNP rs6983267 on chromosome 8q24, which may exert a regulatory influence on the promoter region of the MYC oncogene, was associated with both an increased risk of advanced PC and BC [10]. Therefore, it seems promising to further investigate the clinical significance of these risk SNPs on chromosome 8q24 in patients with concomitant BC and PC with regard to the risk of recurrence after RC. Therefore, the aim of this study was to investigate the impact of distinct SNPs in the promoter region of genes in the 8q24 chromosome region on the risk of BC recurrence after RC.

2. Material and Methods

2.1. Patient cohort

Ethical approval was obtained from the local ethics committee Tübingen (No. 118/2010BO2/No. 677/2012BO2). From the institutional cystectomy database, a total of 36 consecutive patients (median age: 70 years, range: 52–85) were identified who underwent RC with pelvic lymph node dissection for BC without perioperative chemotherapy between 2003 and 2009 and exhibited incidental PC at RC. Patients were included when they were followed up at regular intervals

CONTACT Georgios Gakis georgios.gakis@gmail.com Department of Urology and Pediatric Urology, University Hospital of Würzburg, Oberdürrbacher Strasse 6, Würzburg, 97080, Germany

with cross-sectional imaging and had archived tissue material sufficient for genetic analysis.

2.2. Clinical and histopathological assessment

The clinical and pathologic records were reviewed with regard to age and the number of lymph nodes removed at RC. For BC, pathologic tumor and nodal stage, presence of soft-tissue surgical margins (STSMs), lymphovascular invasion, and tumor grade were re-assessed. For incidental PC, the following clinical and histological parameters were evaluated: pathologic tumor and nodal stage, STSMs, and Gleason pattern. The histologic assessment was conducted according to the 2002 TNM classification approved by the Union International Contre le Cancer (UICC) [11], the WHO classification of 1973 [12] as well as the ISUP classification of 2005 [12]. The histopathologic identification of tumor-free lymph nodes and histological re-assessment of all specimens was conducted in a blinded fashion by an experienced uropathologist (S.P.). Furthermore, the minor allele with the exact location on the chromosome and base position was recorded along with its minor allelic frequency in the present cohort and the normal population [13]. A dominant model of inheritance was assumed in terms of the phenotypical penetrance of the minor allele. Based on literature search [5,7,9,10], the following SNPs located in genes of the 8q24 chromosome region were selected for investigation: PSCA (rs2294008, rs2978974, rs1045531, and rs3736001), MYC (rs6983267), FXBO32 (rs7830622), and MIR151A (rs14974929).

2.3. DNA-sequencing

Allele types were determined using tumor-free lymph node tissue collected during lymph node dissection at RC. First, the formalin-fixed, paraffin-embedded tumor-free lymph node tissue was dissolved using xylole solution. Subsequently, DNA was isolated using the QIAamp® DNA FFPE Tissue Kit (QIAGEN Cat. No. 56404, Hilden, Germany). In the following, specific primers were designed targeting the selected risk SNPs using Primer 3® software (http://primer3.wi.mit.edu). The exact primer lengths were matched using the genome database UCSC (http://genome.ucsc.edu/cgi-bin/hgBlat?gsid=337309609&command=start), to adjust these primers for the human genome. In the following, polymerase-chain-reaction (PCR) was performed using a Veriti™ 96-Well Fast Thermal Cycler and Ampli Taq Gold® Fast PCR Master Mix. Enzymatic purification of the PCR product was performed using Erein® solution (Applied Biosystems, Darmstadt, Germany). For DNA analysis, the Sanger sequencing method was performed using ABI Prism 3730xl DNA Analyzer® and BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Darmstadt). This method is based on the selective incorporation of fluorescent, chain-terminating dideoxynucleotides by DNA polymerases during DNA replication. Hereafter, the base sequence can be determined by separating the different fluorescently labeled termination nucleotides [14].

2.4. Follow-up

Patient charts were reviewed to determine clinical outcomes. In general, patients were examined post-operatively every three to four months for the first year, semiannually for the second and third years, and annually thereafter. Follow-up examinations included cross-sectional imaging in all patients. In addition to physical examination with laboratory testing, intravenous pyelography, urethro-pouchoscopy, urine cytology, urethral washings, and bone scintigraphy were carried out if indicated. Disease recurrence was defined as either local when located in the surgical bed or distant in distant organs. Urethral or upper tract recurrence was defined as an endoscopically confirmed tumor in the urethra or upper urinary tract, respectively [15]. Clinical outcomes were measured from the date of RC to the date of first documented recurrence or the date of the last follow-up when the patient had not experienced disease recurrence. For BC, the median follow-up based on cross-sectional imaging was 26 months (range: 4–68).

2.5. Statistical analysis

For univariable analysis, the Chi-Square/Fisher Exact test was used for nominal data and the Mann–Whitney rank-sum test for scaled data. Kaplan–Meier analysis was used to estimate BC-specific RFS. p-Values are two-sided and $p < 0.05$ was considered significant. Values are given as mean ± S.E.M. for normally distributed data or as median (interquartile range, total range) for non-normally distributed data.

3. Results

The pathologic characteristics of the 36 patients with concomitant BC and PC are given in Table 1. The median age was 70 years (52–85). Regarding SNPs rs3736001 and rs14974929, the corresponding risk allele was not detected in any patient, so these SNPs were excluded from further correlation analysis (see Table 2).

Univariable analysis revealed no significant association between the tested SNPs and the presence of positive lymph nodes while a slight trend toward significance was noted for rs2978974 with regard to the presence of lymph node metastatic disease at RC ($p = 0.13$).

After a median follow-up of 26 months (3–80), 17 of the 36 patients (47.2%) developed local and/or distant recurrence after RC with a median time to recurrence of 7 months (3–54). The 3-year BC-specific RFS and OS were 49 and 62%, respectively. In Kaplan-Meier analysis, advanced pathologic tumor ($p = 0.004$) and nodal stage ($p < 0.001$), and positive soft-tissue surgical margins ($p < 0.001$) were risk factors for decreased BC-specific RFS. Patients exhibiting rs2978974 as a minor allelic variant of the PSCA gene (CT/TT) had worse RFS (32 *vs.* 75%, $p = 0.015$) compared with the patients exhibiting the wildtype genotype (CC). No significant associations were found for the other tested SNPs in terms of RFS.

4. Discussion

In the present study, we aimed to investigate whether risk SNPs of the 8q24 chromosome region may be associated with oncologic outcomes after RC for BC. Therefore, we decided to investigate these effects in a cohort of patients with concomitant BC and PC. Incidental PC is detected in up to 60% of patients undergoing RC [16], and the incidence of MIBC is higher in men than in women. From a genetic point of view, this group of patients can therefore be regarded as a particularly informative collective for further investigation of the theory of androgen-sensitive BC at the predisposing level. While the number of included patients is admittedly low, we found that pathologic tumor and nodal stage as well as STSM were associated with RFS. This suggests the representativeness of the cohort in terms of the oncologic outcomes compared with large series [17]. Regarding the median follow-up period of 26 months, it should be noted that this can be considered adequate based on the median occurrence of local or systemic BC recurrence after 7–18 months in landmark studies [17].

In the present analysis, we investigated four SNPs in the PSCA gene (rs2294008, rs2978974, rs1045531, and rs3736001) that might have a regulatory influence on the PSCA promoter activity based on their gene position [5,7,9]. We found that rs2978974 was associated with inferior BC-specific RFS. The PSCA gene is located on chromosome 8q24.3 and spans 12,420 base pairs [18]. The corresponding PSCA mRNA transcript is composed of three exons (PSCA123). It encodes a glycoprotein consisting of 123 amino acids, which shows altered expression as an epithelial surface antigen on prostate, urothelial, pancreatic, and gastric carcinoma cells [19,20]. The androgen-responsive element (ARE) in the promoter region of the PSCA gene is ~300 bp long. It is located ~3 kb downstream of the transcription start site and ~2.7 kb upstream of the first exon of the PSCA gene [8]. In previous GWAS, rs2978974 and rs2294008 were found to be associated with an increased risk of developing BC [5,7] and carrying both risk alleles (rs2294008 and rs2978974) significantly increased the risk of developing BC [7]. The SNP rs2978974 is located in a non-coding initial region of the first exon of the PSCA gene, whereas rs2294408 is located in the coding portion of the first exon. Examination of a 100 kb DNA segment around the SNP rs2294008 in 5393 BC patients and 7324 control subjects revealed that heterozygous or homozygous carrier of the SNP rs2978974 (CT/TT *vs.* CC) had a significantly higher risk for BC [7]. This result suggests that the SNP rs2978974 has a dominant function compared to the wild-type allele. Similarly, the results of the present study show that at least the heterozygous carriage of the SNP rs2978974 is associated with a significantly increased risk of BC recurrence assuming a dominant mode of inheritance. The present work did not provide evidence that the SNP rs2294008

Table 1. Pathological tumor characteristics of the 36 patients with concomitant bladder and prostate cancer (Leg.: BC: bladder cancer; PC: prostate cancer; STSMs: soft-tissue surgical margins; LV: lymphovascular invasion).

Parameter (BC)	No. of patients	Parameter (PC)	No. of patients
pT-stage		pT-stage	
pT1	1	pT2a	24
pT2a	11	pT2b	3
pT2b	6	pT2c	8
pT3a	5	pT3a	0
pT3b	5	pT3b	0
pT4a	7	pT4	1
pT4b	1		
pN-stage		pN-stage	
pNX	1	pNX	1
pN0	24	pN0	35
pN1	3	pN1	0
pN2	8		
pN3	0		
STSMs		STSMs	
pRX	1	pRX	0
pR0	32	pR0	34
pR+	3	pR1	2
Tumor grade		Gleason-Score	
GX	1	4	6
G1	0	5	11
G2	8	6	8
G3	27	7a	7
		7b	1
		8	2
		9	1
		10	0
LV-status			
LVX	0	–	–
LV0	22	–	–
LVI	14	–	–
cM-stage		–	–
cM0	35	–	–
cM1	1 (osseous, osteolytic)	–	–

Table 3. Univariate analysis of the genotypes of the investigated SNPs and the CAG repeat of the AR gene and presence of node-positive BC disease in the 36 patients with concomitant BC and PC in (assumed) dominant mode of inheritance.

Parameter	*p* (dominant)	OR (95%-CI) dominant
rs2294008 (T)	0.69	0.61 (0.13–2.88)
rs2978974 (T)	0.13	4.5 (0.80–25.35)
rs1045531 (A)	0.68	0.58 (0.13–2.71)
rs3736001 (A)	–	–
rs6983267 (T)	1.0	1.10 (0.22–5.40)
rs7830622 (C)	–	–
rs14974929 (G)	–	–

Table 2. Localization and minor allelic frequency (MAF) of the investigated SNPs in the human genome in patients with BC and PC compared to the normal population (13) (Leg.: A: adenine; C: cytosine; G: guanine; T: thymine).

SNP (minor allele)	Chromosome	Gene	Base position	MAF (present cohort	MAF (normal population)
rs2294008 (T)	8q24.3	PSCA	143,761,931	0.4571	0.4322
rs2978974 (T)	8q24.3	PSCA	143,751,864	0.3472	0.3645
rs1045531 (A)	8q24.3	PSCA	143,763,547	0.4722	0.4272
rs3736001 (A)	8q24.3	PSCA	143,762,307	0	0.0307
rs6983267 (T)	8q24.21	MYC	128,413,305	0.4722	0.4364
rs7830622 (C)	8q24.13	FXBO32	124,542,485	0.0555	0.0746
rs14974929 (G)	8q24.3	MIR151A	55,016,299	0	0.0018

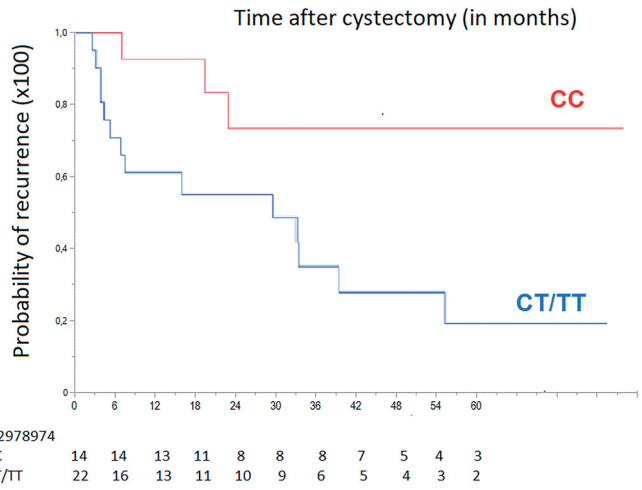

Figure 1. Kaplan–Meier analysis on BC-specific RFS in the 36 patients with concomitant BC and PC as a function of the minor allelic variant (T) rs2978974 of the PSCA gene (CC *vs.* CT/TT). The number of patients at risk of BC recurrence at specific post-operative time intervals is shown below the graph.

is associated with an increased risk of recurrence. Yet, the manner in which the exchange of a single base pair can influence PSCA gene activity was demonstrated in the study by Wang et al. Replacement of the corresponding base pair in the wild-type haplotype (rs2294008 C to T) in UP-H1 BC cell lines decreased PSCA promoter activity, whereas the reverse replacement (rs2294008 T to C) in turn increased the same [21].

In contrast, a recent GWAS reported that rs2294008 resulted in increased PSCA123 mRNA levels, whereas the presence of the SNP rs2978974 had no effect on PSCA123 mRNA expression [7]. However, rs2978974 was shown to condition the formation of an altered PSCA mRNA transcript (PSCA1a2). This observation suggests that this SNP may have an impact on PSCA mRNA expression. A possible explanation would be that these SNPs do not only cause a change in promoter activity, but also different mRNA products with altered biological function through alternative splicing events. At this point, it should be noted that the PSCA protein truncated by nine amino acids in the presence of rs2294008 risk allele results in decreased PSCA protein expression but does not alter its functionality [22].

There is evidence that the PSCA expression on tumor cells can be regulated by the humoral and cellular immune systems. In prostate and pancreatic cancer, preclinical studies have demonstrated that regulation of the PSCA expression can be achieved by the use of tumor vaccines (mediated by tumor antigen-loaded dendritic cells), monoclonal antibodies, or antibody-associated toxic substances [23,24]. A PSCA vaccination study demonstrated a clinical response in the form of prolongation of PSA doubling time in patients with hormone-refractory PC [25]. LY-6 family proteins have been implicated in the transmission of cell signaling during differentiation, maturation, and activation of T lymphocytes. These proteins include PSCA and the CD59 molecule, which protects tumor cells from complement-associated cell lysis [26]. Studies on the BC cell line SW870 have shown that pharmacological downregulation of PSCA expression *via* doxycycline-regulated si-RNA results in cell growth inhibition [27]. In this study, analysis of other deregulated genes revealed that, in particular, genes downstream of the interferon-alpha/beta receptor, MHC class I receptors, Toll-like receptor (TLR) signaling pathway, and interleukin-1 pathway were also activated [27]. However, in humans, the T cell-mediated cytotoxicity of PSCA-positive tumor cells and potential side effects of siRNA treatment has not been adequately studied. Another problem is the fact that antibody-mediated CD8 cell cytotoxicity is hampered due to the lack of antibody-specific receptors on the surface of T8 cells [28]. In contrast, bispecific antibodies against PSCA represent a promising option to combine the humoral and cytotoxic potential of the immune system [29]. It was demonstrated that bispecific anti-CD3 anti-PSCA antibodies lead to a more effective CD8 cell-mediated lysis of PC cells and do not result in a non-specific activation of the immune system. This observation suggests that bispecific antibodies against PSCA can be used systemically in humans without increased risk of severe side effects [28].

However, the response rate of anti-PSCA immunotherapy in BC critically depends on PSCA expression. A recent study investigated PSCA expression in relation to the presence of the SNP rs2294008. This study showed that carriers of this allelic missense variant had stronger PSCA expression than carriers of the CC genotype. This effect was strongest in non-muscle-invasive BC stages (pTa-T1) [30]. Therefore, it seems reasonable to develop antibody therapy against the rs2978974-associated PSCA mRNA transcript (PSCA1a2) when selecting high-risk patients for BC recurrence after RC and to further investigate its efficacy in carriers of the SNP rs2978974 within clinical trials. In conclusion, determining the carriage of risk SNPs in the PSCA gene could improve the prediction of an anti-PSCA therapy in patients with invasive BC and offers new perspectives for improving the prognosis of patients with locally advanced BC.

In conclusion, the present results support the hypothesis that the minor allelic variant rs2978974 of the PSCA gene predisposes to metastatic BC recurrence in patients with concomitant BC and PC. Further studies with larger numbers of patients are needed to confirm these findings.

Acknowledgments

We thank Marita Munz for the technical support during the study

Disclosure statement

All authors report no conflicts of interest in relation to this study.

References

[1] Gakis G, Stenzl A. Gender-specific differences in muscle-invasive bladder cancer: the concept of sex steroid sensitivity. World J Urol. 2013;31(5):1059–1064.

[2] Gakis G, Stenzl A, Renninger M. Evolution of the concept of androgen-sensitive bladder cancer. Scand J Urol. 2013;47(3):173–178.

[3] Chu LW, Meyer TE, Li Q, et al. Association between genetic variants in the 8q24 cancer risk regions and circulating levels of androgens and sex hormone-binding globulin. Cancer Epidemiol Biomarkers Prev. 2010;19(7):1848–1854.

[4] Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet. 2007;39(5):645–649.
[5] Wu X, Ye Y, Kiemeney LA, et al. Genetic variation in the prostate stem cell antigen gene PSCA confers susceptibility to urinary bladder cancer. Nat Genet. 2009;41(9):991–995.
[6] Ishak MB, Giri VN. A systematic review of replication studies of prostate cancer susceptibility genetic variants in high-risk men originally identified from genome-wide association studies. Cancer Epidemiol Biomarkers Prev. 2011;20(8):1599–1610.
[7] Fu YP, Kohaar I, Rothman N, et al. Common genetic variants in the PSCA gene influence gene expression and bladder cancer risk. Proc Natl Acad Sci USA. 2012;109(13):4974–4979.
[8] Jain A, Lam A, Vivanco I, et al. Identification of an androgen-dependent enhancer within the prostate stem cell antigen gene. Mol Endocrinol. 2002;16(10):2323–2337.
[9] Joung JY, Lee YS, Park S, et al. Haplotype analysis of prostate stem cell antigen and association with prostate cancer risk. J Urol. 2011;185(6):2112–2118.
[10] Wokolorczyk D, Gliniewicz B, Sikorski A, et al. A range of cancers is associated with the rs6983267 marker on chromosome 8. Cancer Res. 2008;68(23):9982–9986.
[11] Sobin LH, G MK, Wittekind C. TNM classification of malignant tumors. Vol. 7. Oxford: Wiley-Blackwell; 2002.
[12] Epstein JI, Allsbrook WC Jr., Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma. Am J Surg Pathol. 2005;29(9):1228–1242.
[13] , Altshuler DM, Gibbs RA, International HapMap C, et al. Integrating common and rare genetic variation in diverse human populations. Nature. 2010;467(7311):52–58.
[14] Metzker ML. Sequencing technologies – the next generation. Nat Rev Genet. 2010;11(1):31–46.
[15] Gakis G, Black PC, Bochner BH, et al. Systematic review on the fate of the remnant urothelium after radical cystectomy. Eur Urol. 2017;71(4):545–557.
[16] Damiano R, Di Lorenzo G, Cantiello F, et al. Clinicopathologic features of prostate adenocarcinoma incidentally discovered at the time of radical cystectomy: an evidence-based analysis. Eur Urol. 2007;52(3):648–657.
[17] Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19(3):666–675.
[18] Reiter RE, Sato I, Thomas G, et al. Coamplification of prostate stem cell antigen (PSCA) and MYC in locally advanced prostate cancer. Genes Chromosom Cancer. 2000;27(1):95–103.
[19] Bahrenberg G, Brauers A, Joost HG, et al. Reduced expression of PSCA, a member of the LY-6 family of cell surface antigens, in bladder, esophagus, and stomach tumors. Biochem Biophys Res Commun. 2000;275(3):783–788.
[20] Gu Z, Thomas G, Yamashiro J, et al. Prostate stem cell antigen (PSCA) expression increases with high gleason score, advanced stage and bone metastasis in prostate cancer. Oncogene. 2000; 19(10):1288–1296.
[21] Wang S, Tang J, Wang M, et al. Genetic variation in PSCA and bladder cancer susceptibility in a Chinese population. Carcinogenesis. 2010;31(4):621–624.
[22] , Sakamoto H, Yoshimura K, Saeki N, et al. Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer. Nat Genet. 2008;40(6):730–740.
[23] Saffran DC, Raitano AB, Hubert RS, et al. Anti-PSCA mAbs inhibit tumor growth and metastasis formation and prolong the survival of mice bearing human prostate cancer xenografts. Proc Natl Acad Sci USA. 2001;98(5):2658–2663.
[24] Gu Z, Yamashiro J, Kono E, et al. Anti-prostate stem cell antigen monoclonal antibody 1G8 induces cell death *in vitro* and inhibits tumor growth *in vivo* via a Fc-independent mechanism. Cancer Res. 2005;65(20):9495–9500.
[25] Waeckerle-Men Y, Uetz-von Allmen E, Fopp M, et al. Dendritic cell-based multi-epitope immunotherapy of hormone-refractory prostate carcinoma. Cancer Immunol Immunother. 2006;55(12): 1524–1533.
[26] Gorter A, Meri S. Immune evasion of tumor cells using membrane-bound complement regulatory proteins. Immunol Today. 1999;20(12):576–582.
[27] Marra E, Uva P, Viti V, et al. Growth delay of human bladder cancer cells by prostate stem cell antigen downregulation is associated with activation of immune signaling pathways. BMC Cancer. 2010;10:129.
[28] Feldmann A, Stamova S, Bippes CC, et al. Retargeting of T cells to prostate stem cell antigen expressing tumor cells: comparison of different antibody formats. Prostate. 2011;71(9):998–1011.
[29] Buhler P, Molnar E, Dopfer EP, et al. Target-dependent T-cell activation by coligation with a PSMA $\times$ CD3 diabody induces lysis of prostate cancer cells. J Immunother. 2009;32(6):565–573.
[30] Kohaar I, Porter-Gill P, Lenz P, et al. Genetic variant as a selection marker for anti-prostate stem cell antigen immunotherapy of bladder cancer. J Natl Cancer Inst. 2013;105(1):69–73.