

## Original Article

# Associations between polymorphisms in the IL-4 and IL-4 receptor genes and urinary carcinomas: a meta-analysis

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**Abstract:** To evaluate the association between polymorphisms of interleukin-4 (*IL-4*) and IL-4 receptor (*IL-4R*) genes and risk of renal cell cancer (RCC), bladder cancer (BC), and prostate cancer (PC) based on meta-analysis. PubMed, Web of Science and SpecialSCI™ were searched for studies published up to May 2014 that reported the association between *IL-4* or *IL-4R* and RCC, BC or PC risk. Odds ratio (OR)/Hazard ratio (HR) and 95% confidence interval (CI) were analyzed to evaluate the association. Meta-analysis showed that the *IL-4R* polymorphism rs1805010 was associated with increased RCC risk (CC/CT vs. TT: OR=1.266, 95% CI 1.09-1.472, P=0.002). The *IL-4* haplotypes, IL4-589T and IL4-33T, were associated with higher survival rate of the patients compared with the haplotype IL4-589C-33C (P<0.05). The *IL-4* polymorphism rs2243250 was associated with an increased risk of developing multiple BCs (OR=2.52, P=0.033). The *IL-4* polymorphisms rs2243228, rs2243250, and rs22272480 were significantly associated with PC risk (rs2243228 CC vs. CA/AA: OR=0.27, 95% CI 0.09-0.84, P=0.03; rs2243350 TT vs. CT/CC: OR=2.16, 95% CI 1.06-4.40, P=0.03, CC vs. CT/TT: OR=1.31, 95% CI 1.05-1.65, P=0.02; rs2227284 TT vs. GT/GG: OR=1.98, 95% CI 1.30-3.00, P=0.001). In addition, *IL-4* polymorphism rs2070874 was associated with PC mortality. Three polymorphisms (rs2070874, rs1805015, and rs1801275) were not associated with RCC, BC, and PC. The *IL-4R* polymorphism rs1805015 might be associated with RCC risk. *IL-4* rs2243250 carriers had increased risk of developing multiple BCs. *IL-4* polymorphisms rs2243228, rs2243250, rs2227284, and rs2070874 were associated with PC risk or mortality.

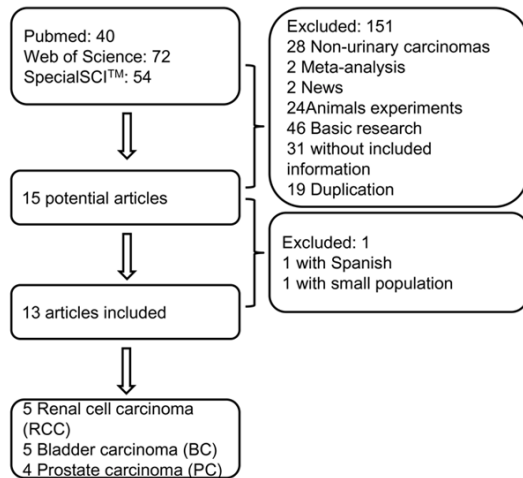
**Keywords:** IL-4, IL-4R, polymorphism, cancer

## Introduction

The cancer incidence is increasing worldwide. It has been estimated that a total of 14.1 million new cases and 8.2 million deaths caused by cancers occurred in 2012 ([http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)). According to the human development index, it is predicted that cancer cases will have been increasing from 12.7 million in 2008 to 22.2 million by 2030 [1]. Cancers are multifactorial diseases involved in complicated interactions of genetic and environment factors [2]. Gene mutation is one of the most important risk factors of cancer. Single nucleotide polymorphisms (SNPs) contribute to carcinogenesis in various ways, such as affecting the function of cytokines involved in immune responses and inflamma-

tory reaction, influencing the binding of nuclear factors with target genes, and inhibiting apoptosis [3, 4].

Interleukin-4 (IL-4), a member of the  $\alpha$ -helical cytokine family, is produced by activated CD4<sup>+</sup> T cells, basophils, and mast cells. IL-4 is the central differentiation factor driving Th2 development, eliminating extracellular pathogens, and inhibiting Th1 differentiation. Therefore, IL-4 plays an important role in surveillance and elimination of transformed cells [5]. Numerous epidemiologic studies have examined the association of IL-4 gene polymorphisms with cancer risk. For example, the *IL-4* -590C>T (rs2243250) polymorphism on the promoter region [6] contributed to threefold higher transcriptional activity both *in vitro* and *in vivo* [7]. This SNP



**Figure 1.** A flow diagram of the selection and disposition of published studies on the association of IL-4 and IL-4R polymorphisms with cancer risks.

has been explored in several types of carcinomas such as oral cancer [8], colorectal cancer [9], and lung cancer [10].

IL-4 receptor (IL-4R) is a heterodimeric complex that can bind to the Th2 cytokines IL-4 and IL-13 [11]. High level expression of IL-4R has been observed in colorectal carcinoma [12]. In addition, polymorphisms of *IL-4R* were involved in the etiology of various cancers, including pancreatic cancer and cervical cancer [13, 14]. In the present study, a systematic meta-analysis was conducted to explore the role of IL-4 and IL-4R polymorphisms in the pathogenesis of RCC, BC and PC.

**Methods**

*Literature search*

Eligible studies up to May 2014 were independently identified and extracted by two investigators from the database of NCBI PubMed, Web of Science and SpecialSCI™. Discrepancies in data interpretation were resolved by discussion, review of the studies, and consultation with two cancer research experts when necessary. The keywords used for literature search are as follows: (IL-4 OR Interleukin-4 OR IL4) AND (SNP OR mutation OR variant OR polymorphism) AND (prostate OR renal OR kidney OR bladder) AND (carcinoma OR cancer OR tumor). The search was not limited to English language articles. In addition, studies cited in the reference lists were also identified by a manual search.

Studies included in our meta-analysis meet the following inclusion criteria: i) studies about SNP(s) of IL-4 and/or IL-4R; ii) patients with renal cancer, prostate cancer or bladder cancer; iii) sufficient genotype distributions for cases and controls so that an odds ratio (OR) with 95% confidence interval (CI) can be assessed. Studies without the number of genotype, but having OR and 95% CI, were also included in the meta-analysis. Of studies published the same case series, we selected the most recent ones with the largest sample size.

*Statistical analysis*

Pooled OR and 95% CI were used to estimate the strength of association between the SNPs of IL-4 and IL-4R and cancer risk.

Heterogeneity was evaluated by a  $\chi^2$ -based Q statistic. Statistical significance was determined as P value less than 0.05. When P value was above 0.05, OR was pooled using the fixed-effect model, otherwise the random effect model was used. The statistical significance of OR was analyzed by Z test and P value less than 0.05 was considered statistically significant.

**Results**

*Database of meta-analysis*

A total of 166 publications were identified after initial screening based on the above criteria. Among these, 15 articles were subjected to further examination after reading the titles and abstracts. Two studies were excluded from the meta-analysis as one published in Spanish and another one that used smaller sample size of cancer patients than other studies. Finally, 13 articles (**Figure 1**) including five studies of renal cancer [11, 15-18], four studies about bladder cancer [19-22], and four studies of prostate cancer were included in this meta-analysis [23-26].

*Quantitative analysis of IL-4 polymorphisms*

Polymorphism *IL-4* C-590T (rs2243250) was identified in two studies of RCC (747 RCC patients and 797 controls) and two studies of BC (954 BC patients and 1245 controls). For RCC cases, the fixed model was used to analyze the patterns of CC vs. CT/TT, CC/CT vs. TT and T vs. C as heterogeneity was not identified in these studies ( $I^2=0\%$ , **Table 1**). No significant

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**Table 1.** The association between polymorphisms in the IL-4/IL-4 receptor gene and urinary carcinomas

SNP	Carcinoma	Pattern	OR/HR (95% CI)	P	Reference
<b>IL-4</b>					
rs2243228	PC	CC vs. CA/AA	0.27 (0.09-0.84)	0.03	[25]
rs2243250	PC	TT vs. CT/CC	2.16 (1.06-4.40)	0.03	[26]
		CC vs. CT/TT	1.31 (1.05-1.65)	0.02	[26]
rs2227284	PC	TT vs. GT/GG	1.98 (1.30-3.00)	0.001	
rs2070874 <sup>#</sup>	PC	CC vs. CT/TT	2.16 (1.27-3.67)	0.005	[24]
			1.27 (1.04-1.56)	0.011	
<b>IL-4R</b>					
rs1805010	RCC	CC vs. CT/TT	1.266 (1.09-1.472)	0.002	[12, 16, 17]
rs2243250 <sup>*</sup>	BC	T vs. C	2.80 (1.08-7.27)	0.031	[21]

Note: The non-significant difference between SNPs of IL-4/IL-4R and cancer was not shown.

<sup>#</sup>This study was a cohort study and the significant difference in different population (Seattle and Swedish). <sup>\*</sup>This SNP was associated with the developing multiple BC.

differences were observed between RCC patients and controls ( $P=0.238$ ,  $P=0.345$  and  $P=0.165$ ). For BC cases, the random model was used to analyze the three patterns as heterogeneity was identified ( $I^2=71.2\%$ ,  $92.5\%$  and  $92.1\%$ ). No significant differences were observed between BC patients and controls ( $P=0.558$ ,  $0.313$  and  $0.319$ ).

### Quantitative analysis of IL-4R polymorphisms

Polymorphisms *IL-4R* rs1805010, rs1805015, and rs1801275 were identified in three studies of RCC, two studies of BC, and one study of PC. A total of 813 RCC patients and 879 controls were included in the studies of *IL-4R* rs1805010 polymorphism. A total of RCC 620 patients and 623 controls were included in the *IL-4R* rs1805015 polymorphism, and 1626 RCC patients and 1758 controls were included in the *IL-4R* rs1801275 polymorphism. The fixed model was used to analyze the rs1805010 polymorphism because heterogeneity was not identified in the pattern of CC vs. CT/TT ( $I^2=21.4\%$ , **Table 1**). Heterogeneity was identified in the pattern of CC/CT vs. TT ( $I^2=84\%$ ) and T vs. C ( $I^2=84.1\%$ ). Significant differences were observed in the pattern of CC vs. CT/TT between RCC patients and controls (OR 1.266, 95% CI 1.09-1.472,  $P=0.002$ ), while no significant was identified in the patterns of CC/CT vs. TT ( $P=0.866$ ) and C vs. T ( $P=0.972$ ). The random model was used to analyze the rs1801275 polymorphism because heterogeneity was identified in the patterns of AA vs. AG/GG

( $I^2=58.8\%$ ), AA/AG vs. GG ( $I^2=32.7\%$ ) and A vs. G ( $I^2=56.7\%$ ). No significant differences were identified in the patterns of AA vs. AG/GG ( $P=0.581$ ), AA/AG vs. GG ( $P=0.669$ ) and A vs. G ( $P=0.483$ ).

A total of 1440 bladder carcinoma patients and 1762 controls were included in the studies of *IL-4R* rs1801275 polymorphism. The random model was used to analyze the rs1801275 polymorphism because heterogeneity was identified

in the patterns of AA vs. AG/GG ( $I^2=65\%$ ) and A vs. G ( $I^2=39.6\%$ ). The fixed model was used to analyze the pattern of AA/AG vs. GG ( $I^2=0\%$ ) because heterogeneity was identified. No significant differences were identified in the patterns of AA vs. AG/GG ( $P=0.554$ ), AA/AG vs. GG ( $P=0.23$ ) and A vs. G ( $P=0.795$ ).

### Other polymorphisms of IL-4 and IL-4R

The *IL-4R* rs1805015 polymorphism was investigated in one study including 620 RCC patients and 623 controls [15]. No significant differences of the genotype distribution of TT, CT, and TT ( $P=0.125$ ), and the C allele ( $P=0.942$ ) were observed between RCC patients and controls. In addition, a cross-sectional single-center study including 80 metastatic RCC patients showed that the promoter region of *IL-4* haplotype (IL4-589T and IL4-33T) was highly associated with the survival rate of RCC patients [18]. The median overall survival decreased 3.5-fold ( $P<0.05$ ) in heterozygote patients carrying *IL-4* haplotype -589T-33T and -589C-33C (3.78 months) compared with homozygote patients carrying *IL-4* haplotype -589C-33C (13.44 months).

In a study of the rs1805015 polymorphism, no significant differences of the genotype distribution (TT, CT and TT) ( $P=0.376$ ) and the C allele ( $P=0.787$ ) were identified between 816 bladder carcinoma patients and 1140 controls [19]. However, a case-control study showed that *IL-4* rs2243250 carriers had an increased risk of

developing multiple bladder carcinomas in the pattern T vs. C (OR 2.80 05% CI 1.08-7.27),  $P=0.031$ ) [20].

In a case-control study of the IL-4 rs2243228 polymorphism, no significant differences of the pattern of CC vs. CA/AA (OR=0.27, 95% CI 0.09-0.84,  $P=0.03$ ) were observed between prostate carcinoma patients and 1351 controls [24]. Significant differences of the genotype distribution of IL-4 polymorphisms rs2243250 and rs2227284 were identified between 825 prostate carcinoma cases and 732 controls [25]. For each polymorphism, ORs of two allele were 1.32 (95% CI 1.08-1.61) and 1.26 (95% CI 1.07-1.48), respectively. The rs2243250 polymorphism was significantly associated with cancer risk in the patterns of TT vs. CT/CC (OR=2.16, 95% CI 1.06-4.40,  $P=0.03$ ) and CC vs. CT/TT (OR=1.31, 95% CI 1.05-1.65,  $P=0.02$ ), whereas rs2227284 was significantly associated with cancer risk only for TT vs. GT/GG (OR=1.98, 95% CI 1.30-3.00,  $P=0.001$ ). In the included cohort study, another IL-4 polymorphism rs2070874 was also associated with the mortality of prostate cancers in different populations (CC vs. CT/TT for the Seattle Cohort: HR=2.16, 95% CI 1.27-3.67,  $P=0.005$ ; For Swedish Cohort: HR=1.27, 95% CI 1.04-1.56,  $P=0.011$ ) [23].

### Discussion

IL-4 and IL-4R play essential roles in the development of many carcinomas. Numerous studies have investigated the association between IL-4 or IL-4R polymorphisms and cancer risk or mortality. In the present study, we performed a meta-analysis including 13 studies to review the association between IL-4 or IL-4R polymorphisms and risk of RCC, bladder carcinoma, and prostate carcinoma.

Our meta-analysis revealed that the IL-4 C-590T variant (polymorphism rs2243250) was not associated with RCC risk, which is not consistent with previous report in which polymorphism rs2243250 was associated with increased RCC risk (TT vs. CC/CT: OR=1.43, 95% CI 1.05-1.95,  $P=0.022$ ) [27]. This discrepancy might be explained by the fact that our meta-analysis included larger population and was based on two studies conducted in China and Spain, respectively. Carcinogenesis is a complex process in which many genes and environ-

mental factors are involved. Therefore, the association of IL-4 polymorphism rs2243250 should be further studied and interpreted with cautions. Regarding the IL-4R polymorphisms, only rs1805010 was associated with significantly decreased RCC risk in the pattern of CC vs. CT/TT. The underlying mechanism of the association of IL-4R polymorphism rs1805010 with decreased RCC was not fully understood. The recent study reported that IL-4R blockade abrogates satellite cells, leading to rhabdomyosarcoma fusion and preventing tumor establishment in muscle-related cancers [28]. In addition, it has also been reported that IL-mediated significant antitumor effects in animal model of human head and neck squamous cell carcinoma [29]. While the association of other polymorphisms of IL-4 and IL-4R with cancer risk was not found in the present study, the survival rate of patients with homozygote for IL4 haplotype -589C-33C was significantly longer than other patients. Probable explanation is that IL4 polymorphisms was in strong linkage with KIF3A that plays a key role in the metastasis of tumor cells and genetic inactivation of KIF3A in mice inhibited renal ciliogenesis and caused polycystic kidney disease [30, 31].

No significant association of IL-4 and IL-4R polymorphisms with bladder carcinoma risk was identified in the present meta-analysis. However, IL-4 polymorphism rs2243250 had a strong association with developing multiple carcinomas in bladder cancer patients. This may be explained by the fact that IL-4 promotes the expansion of Th2 cells in bladder cancer patients and leads to the suppression of Th1 responses [32]. The generation of effector cytotoxic T lymphocytes was required to suppress tumors by lysing cancer cells and subsequently decreasing immune surveillance against tumors [32, 33]. In addition, patients with the IL-4-590 T allele seem to have a higher production of IL-4 [34], which may induce immunosuppression against tumors (Th1 inhibition). Therefore, IL-4 may be involved in cancer cell escape from lymphocyte killing and the development of multiple tumors in bladder urothelium [35].

To the best of our knowledge, this is the first comprehensive meta-analysis investigating the association of IL-4 and IL-4R polymorphisms and prostate carcinoma. Recently, four IL-4



polymorphisms were found to be associated with prostate carcinoma. Three polymorphisms (rs2243228, rs2243250 and rs2227284) were associated with cancer risk and the polymorphism rs2070874 was associated with cancer mortality. The growth of prostate cancer cells depends mainly on hormones, notably androgen. IL-4 may be involved in androgen-independent tumor progression [36-39].

When interpreting the results of the present meta-analysis, several limitations should be considered. First, a limited numbers of studies on the association of IL-4 and IL-4R polymorphisms and RCC, bladder carcinoma, and prostate carcinoma were available, practically in prostate carcinoma. Studies of these polymorphisms in a large number of European countries were not available, especially for RCC. Third, the literature searches were carried out in only three databases (NCBI PubMed, Web of Science and SpecialSCI™), which may miss some important studies in other languages and database.

In summary, our results suggest that the IL-4R polymorphism rs1805015 is associated with RCC risk. IL-4 rs2243250 carriers had an increased risk of developing multiple bladder carcinomas. IL-4 polymorphisms rs2243228, rs2243250, rs2227284, and rs2070874 were associated with prostate cancer risk and mortality. Given the limitations mentioned above, we encourage more studies to further study the association of IL-4 and IL-4R polymorphisms with cancers, which will also contribute to our understanding of the role of IL-4 and IL-4R in carcinogenesis.

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### Disclosure of conflict of interest

None.

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### References

- [1] Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol* 2012; 13: 790-801.
- [2] Pharoah PD, Dunning AM, Ponder BA, Easton DF. Association studies for finding cancer-susceptibility genetic variants. *Nat Rev Cancer* 2004; 4: 850-860.
- [3] Bayley JP, Ottenhoff TH, Verweij CL. Is there a future for TNF promoter polymorphisms? *Genes Immun* 2004; 5: 315-329.
- [4] Imyanitov EN. Gene polymorphisms, apoptotic capacity and cancer risk. *Hum Genet* 2009; 125: 239-246.
- [5] Muller-Hermelink N, Braumuller H, Pichler B, Wieder T, Mailhammer R, Schaak K, Ghoreschi K, Yazdi A, Haubner R, Sander CA, Mocikat R, Schwaiger M, Forster I, Huss R, Weber WA, Kneilling M, Rocken M. TNFR1 signaling and IFN-gamma signaling determine whether T cells induce tumor dormancy or promote multi-stage carcinogenesis. *Cancer Cell* 2008; 13: 507-518.
- [6] Le Beau MM, Lemons RS, Espinosa RR, Larson RA, Arai N, Rowley JD. Interleukin-4 and interleukin-5 map to human chromosome 5 in a region encoding growth factors and receptors and are deleted in myeloid leukemias with a del(5q). *Blood* 1989; 73: 647-650.
- [7] Nakashima H, Miyake K, Inoue Y, Shimizu S, Akahoshi M, Tanaka Y, Otsuka T, Harada M. Association between IL-4 genotype and IL-4 production in the Japanese population. *Genes Immun* 2002; 3: 107-109.
- [8] Gaur P, Mittal M, Mohanti B, Das S. Functional variants of IL4 and IL6 genes and risk of tobacco-related oral carcinoma in high-risk Asian Indians. *Oral Dis* 2011; 17: 720-726.
- [9] Suchy J, Klujesz-Grabowska E, Kladny J, Cybulski C, Wokolorczyk D, Szymanska-Pasternak J, Kurzawski G, Scott RJ, Lubinski J. Inflammatory response gene polymorphisms and their relationship with colorectal cancer risk. *BMC Cancer* 2008; 8: 112.
- [10] Gomes M, Coelho A, Araujo A, Teixeira AL, Catarino R, Medeiros R. Influence of functional genetic polymorphism (-590C/T) in non-small cell lung cancer (NSCLC) development: the paradoxical role of IL-4. *Gene* 2012; 504: 111-115.
- [11] Nakamura E, Megumi Y, Kobayashi T, Kamoto T, Ishitoya S, Terachi T, Tachibana M, Matsuhiro H, Habuchi T, Takechi Y, Ogawa O. Genetic polymorphisms of the interleukin-4 receptor alpha gene are associated with an increasing risk and a poor prognosis of sporadic renal cell

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- carcinoma in a Japanese population. *Clin Cancer Res* 2002; 8: 2620-2625.
- [12] Formentini A, Braun P, Fricke H, Link KH, Henne-Bruns D, Kornmann M. Expression of interleukin-4 and interleukin-13 and their receptors in colorectal cancer. *Int J Colorectal Dis* 2012; 27: 1369-1376.
- [13] Castro FA, Haimila K, Sareneva I, Schmitt M, Lorenzo J, Kunkel N, Kumar R, Forsti A, Kjellberg L, Hallmans G, Lehtinen M, Hemminki K, Pawlita M. Association of HLA-DRB1, interleukin-6 and cyclin D1 polymorphisms with cervical cancer in the Swedish population—a candidate gene approach. *Int J Cancer* 2009; 125: 1851-1858.
- [14] Olson SH, Orlow I, Simon J, Tommasi D, Roy P, Bayuga S, Ludwig E, Zauber AG, Kurtz RC. Allergies, variants in IL-4 and IL-4R alpha genes, and risk of pancreatic cancer. *Cancer Detect Prev* 2007; 31: 345-351.
- [15] Chu H, Wang M, Yan F, Zhong D, Shi D, Ma L, Pan X, Qin C, Yin C, Zhang Z. Polymorphisms in the IL-13 and IL-4R genes are associated with the development of renal cell carcinoma. *Ann Oncol* 2012; 23: 2114-2121.
- [16] Mohan S, Mohanasenthil, Paul SF, Shroff S, Venkatesan V. Interleukin-4-receptor alpha gene polymorphism and the risk of renal cell carcinoma in a South Indian population. *Asian Pac J Cancer Prev* 2009; 10: 295-298.
- [17] Cozar JM, Romero JM, Aptsiauri N, Vazquez F, Vilchez JR, Tallada M, Garrido F, Ruiz-Cabello F. High incidence of CTLA-4 AA (CT60) polymorphism in renal cell cancer. *Hum Immunol* 2007; 68: 698-704.
- [18] Kleinrath T, Gassner C, Lackner P, Thurnher M, Ramoner R. Interleukin-4 promoter polymorphisms: a genetic prognostic factor for survival in metastatic renal cell carcinoma. *J Clin Oncol* 2007; 25: 845-851.
- [19] Chu H, Ma L, Wang M, Shi D, Qin C, Yuan L, Yin C, Zhang Z. The polymorphisms of IL-4, IL-4R and IL-13 genes and bladder cancer risk in a Chinese population: a case-control study. *Mol Biol Rep* 2012; 39: 5349-5357.
- [20] Lima L, Silva J, Amaro T, Morais A, Lopes C, Medeiros R, Videira PA, Santos L. IL-4 and TNF-alpha polymorphisms are associated with risk of multiple superficial tumors or carcinoma in situ development. *Urol Int* 2011; 87: 457-463.
- [21] Yang H, Gu J, Lin X, Grossman HB, Ye Y, Dinney CP, Wu X. Profiling of genetic variations in inflammation pathway genes in relation to bladder cancer predisposition. *Clin Cancer Res* 2008; 14: 2236-2244.
- [22] Tsai FJ, Chang CH, Chen CC, Hsia TC, Chen HY, Chen WC. Interleukin-4 gene intron-3 polymorphism is associated with transitional cell carcinoma of the urinary bladder. *Bju Int* 2005; 95: 432-435.
- [23] Lin DW, FitzGerald LM, Fu R, Kwon EM, Zheng SL, Kolb S, Wiklund F, Stattin P, Isaacs WB, Xu J, Ostrander EA, Feng Z, Gronberg H, Stanford JL. Genetic variants in the LEPR, CRY1, RNASEL, IL4, and ARVCF genes are prognostic markers of prostate cancer-specific mortality. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 1928-1936.
- [24] Kwon EM, Salinas CA, Kolb S, Fu R, Feng Z, Stanford JL, Ostrander EA. Genetic polymorphisms in inflammation pathway genes and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 923-933.
- [25] Tindall EA, Severi G, Hoang HN, Ma CS, Fernandez P, Southey MC, English DR, Hopper JL, Heyns CF, Tangye SG, Giles GG, Hayes VM. Comprehensive analysis of the cytokine-rich chromosome 5q31.1 region suggests a role for IL-4 gene variants in prostate cancer risk. *Carcinogenesis* 2010; 31: 1748-1754.
- [26] Kesarwani P, Ahirwar DK, Mandhani A, Mittal RD. Association between -174 G/C promoter polymorphism of the interleukin-6 gene and progression of prostate cancer in North Indian population. *Dna Cell Biol* 2008; 27: 505-510.
- [27] Wang JY, Zhou YQ, Li XX, Jin X, Wang LL, Lei L, Zhou Y, Lu J, Zeng X, Dan HX, Liao G, Chen QM. Associations between three polymorphisms in the interleukin-4 receptor gene and risk of cancer: a meta-analysis. *Asian Pac J Cancer Prev* 2012; 13: 6227-6232.
- [28] Li G, Kikuchi K, Radka M, Abraham J, Rubin BP, Keller C. IL-4 receptor blockade abrogates satellite cell: rhabdomyosarcoma fusion and prevents tumor establishment. *Stem Cells* 2013; 31: 2304-2312.
- [29] Strome SE, Kawakami K, Alejandro D, Voss S, Kasperbauer JL, Salomao D, Chen L, Maki RA, Puri RK. Interleukin 4 receptor-directed cytotoxic therapy for human head and neck squamous cell carcinoma in animal models. *Clin Cancer Res* 2002; 8: 281-286.
- [30] Yanagawa T, Watanabe H, Takeuchi T, Fujimoto S, Kurihara H, Takagishi K. Overexpression of autocrine motility factor in metastatic tumor cells: possible association with augmented expression of KIF3A and GDI-beta. *Lab Invest* 2004; 84: 513-522.
- [31] Lin F, Hiesberger T, Cordes K, Sinclair AM, Goldstein LS, Somlo S, Igarashi P. Kidney-specific inactivation of the KIF3A subunit of kinesin-II inhibits renal ciliogenesis and produces polycystic kidney disease. *Proc Natl Acad Sci U S A* 2003; 100: 5286-5291.
- [32] Agarwal A, Verma S, Burra U, Murthy NS, Mohanty NK, Saxena S. Flow cytometric analysis of Th1 and Th2 cytokines in PBMCs as a parameter of immunological dysfunction in patients of superficial transitional cell carcinoma

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- of bladder. *Cancer Immunol Immunother* 2006; 55: 734-743.
- [33] Knutson KL, Disis ML. Tumor antigen-specific T helper cells in cancer immunity and immunotherapy. *Cancer Immunol Immunother* 2005; 54: 721-728.
- [34] Rosenwasser LJ, Klemm DJ, Dresback JK, Inamura H, Mascali JJ, Klinnert M, Borish L. Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. *Clin Exp Allergy* 1995; 25 Suppl 2: 74-78, 95-96.
- [35] Tan TT, Coussens LM. Humoral immunity, inflammation and cancer. *Curr Opin Immunol* 2007; 19: 209-216.
- [36] Lee SO, Chun JY, Nadiminty N, Lou W, Feng S, Gao AC. Interleukin-4 activates androgen receptor through CBP/p300. *Prostate* 2009; 69: 126-132.
- [37] Lee SO, Lou W, Hou M, Onate SA, Gao AC. Interleukin-4 enhances prostate-specific antigen expression by activation of the androgen receptor and Akt pathway. *Oncogene* 2003; 22: 7981-7988.
- [38] Lee SO, Pinder E, Chun JY, Lou W, Sun M, Gao AC. Interleukin-4 stimulates androgen-independent growth in LNCaP human prostate cancer cells. *Prostate* 2008; 68: 85-91.
- [39] Takeshi U, Sadar MD, Suzuki H, Akakura K, Sakamoto S, Shimbo M, Suyama T, Imamoto T, Komiya A, Yukio N, Ichikawa T. Interleukin-4 in patients with prostate cancer. *Anticancer Res* 2005; 25: 4595-4598.