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Polymorphism Analysis of TRAIL Gene and Correlation TRAIL Expression in Prostate Cancer

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1. Introduction

Prostate cancer (PCa) is the most common male non-dermatological cancer in Europe and the United States of America (USA), and the sixth leading cause of cancer related-deaths, accounting for 14% (903,500) of total new diagnosed cancer cases and 6% (258,400) of whole cancer deaths in males in 2008 [1]. Because the increased use of screening techniques testing serum concentrations of prostate-specific antigen (PSA) has meant that PCa is more commonly diagnosed and can be detected at an earlier stage, the incidence rates recorded primarily in the developed countries, such as Oceania, Europe and North America, were hight. In contrast, males of African individuals in the Caribbean region have the highest PCa mortality rates in the world, which is thought to reflect partly difference in genetic susceptibility [2, 3].

Death rates for PCa have been decreasing in many developed countries, including Australia, Canada, USA, the United Kingdom, Italy and Norway in part due to the improved treatment with curative intent [4-6]. Recently, one European-based trial on the efficacy of PSA testing could reduce the rate of death from PCa by 20% [7]. In contrast to the trends of western countries, incidence and mortality rates are rising in several Asian and central/eastern-European countries, such as Japan, China and Poland, suggesting an increasingly westernized lifestyle in these regions [4, 5]. The underlying etiology of PCa remains poorly understood, with both genetic predisposition and environmental factors (diet, lifestyle, older age, race, family history and hormone) likely to play an important role [8-10]. Despite this strong evidence for a genetic component in PCa, little progress has been made to identify a major gene or genes [11].

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is a novel member of the TNF super-family and was first identified by Wiley in 1995 [12]. TRAIL is mapped to the long arm of chromosome 3q26 in humans and is composed of five exons. It encodes 1.77 kb mRNA. Similar to FasL, TRAIL is also a type II membrane protein which induces apoptosis in a wide variety of cancer cells and spares normal cells [12]. TRAIL-induced apoptosis is a multi-step process: it binds to death receptor 4 (DR4) and DR5 cell surface receptors leading

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to the formation of the death inducing signaling complex (DISC) that recruits caspase-8 via the adaptor protein Fas-associated with death domain protein (FADD). The formation of DISC and recruitment of caspase-8 leads to proteolytic activation of caspase-3 and caspase-7 leading to DNA fragmentation and apoptosis [13-15] (Fig. 1).

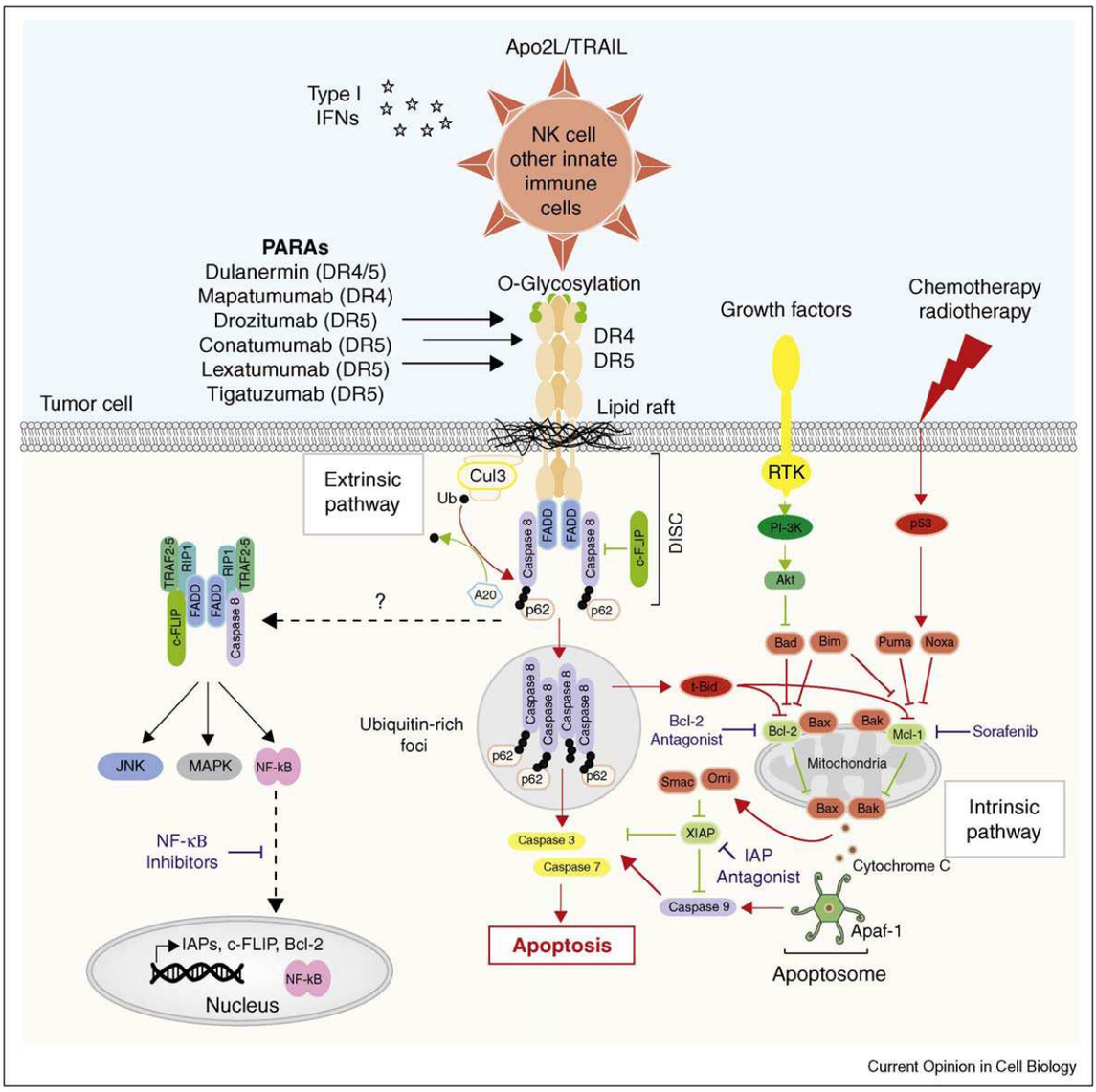

Fig. 1. TRAIL pathway for cancer therapy. DR4 and DR5 activation by PARAs (either trimeric rhApo2L/TRAIL or agonistic DR4 or DR5-specific antibodies) or Apo2L/TRAIL expressed by innate immune cells. FADD is recruited to DR4 or DR5 located within lipid raft containing regions of the membrane, which promotes receptor clustering and autocatalytic processing of the apoptosis initiating proteases caspase-8 or caspase-10 to form the active DISC. Caspase-8 can be polyubiquitylated at the DISC by a cullin-3/Rbx1-based E3 ubiquitin ligase, which facilitates caspase-8 activation. This process is negatively regulated by the de-ubiquitinating enzyme, A20. The signaling adaptor p62 can bind to ubiquitilated caspase-8 and translocate it to ubiquitin-rich foci, which may also enhance its activity. In many cancer cells, proapoptotic

signaling involves the mitochondrial pathway via caspase-8-mediated cleavage of Bid to t-Bid. Proapoptotic signaling through the intrinsic pathway is further regulated by pro apoptotic and anti apoptotic members of the Bcl-2 family. Receptor tyrosine kinase (RTK) signaling and chemotherapy or radiotherapy can further modulate the intrinsic proapoptotic pathway through targeting Bcl-2 family members. Under certain circumstances, DR4 or DR5 signaling can promote alternative signaling pathways such as JNK, MAPK or NF_kB, which may require recruitment of RIP1 and TRAF2 or TRAFs5 to form secondary signaling complexes. Depicted in blue are inhibitors that may enhance proapoptotic signaling by PARAs by targeting mechanisms of resistance in tumor cells. (This picture was cited from Yang et al. [50] Current Opinion in Cell Biology. 2010)

Several single nucleotide polymorphisms (SNPs) present along the TRAIL gene located in the 3q26 region have been found in both healthy and disease individuals, including four SNPs in the 5′ regulatory region [16], two SNPs within exons, and five SNPs in the 3′ untranslated regions[17-18]. TRAIL gene polymorphisms were also identified in patients with multiple sclerosis [19, 20] and fatty liver disease [21].

Recently, a SNP of -716A>G polymorphism (rs12488654) in the promoter region of TRAIL gene has been found to be associated with breast cancer with functional implications both in vitro and vivo studies [22]. To date, there have been no data about the association between this polymorphism and PCa, so we first explored the role of the TRAIL A>G polymorphism in PCa patients in southern Chinese Han descent. Moreover, we detected the serum levels of TRAIL expression with different genotypes in cases to characterize the functional consequences of TRAIL -716 A>G polymorphism.

2. Materials and methods

2.1 Study population

One hundred and eighty-seven PCa patients were newly diagnosed between November 2009 and May 2010 in the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital) in Nanjing, China. All PCa cases were between 51 and 94 years of age and were diagnosed with the disease within the last one year; all controls were between 47 and 96 years of age. All cases were diagnosed with PCa through needle biopsy (ultrasoundguided transrectal needle biopsy of prostate, 13-fold biopsy) or operation (radical prostatectomy and transurethral resection of the prostate). All the patients were southern Chinese Han descent. The control group (n = 237) was age-matched and the subjects were healthy checkup examinees without cancer history and were collected in the same period. Controls were excluded if they ever had abnormal appearance of pathology, abnormal prostate-specific antigen test (i.e., ≥ 4 ng/ml), abnormal digital rectal examination, other previous cancer diagnosis, symptom of any prostate disease or abnormal appearance of other auxiliary examination including computed tomography urography (CTU), magnetic resonance urography (MRU), positron emission tomographic (PET), transrectal ultrasonography and so on.

After informed consent was obtained, 2 ml peripheral blood sample was collected and each subject was asked to finish a questionnaire including age, weight, height, race, tobacco use, alcohol use, family history of cancer and so on. In our present research, smoking more than five cigarettes per day for more than 5 years was defined as smoking; drinking habit was defined as drinking at least three times per week and lasting more than 10 years; family history of cancer was defined as cancer in first-degree relatives (parents, siblings, or

children); disease stage was determined by pathologic findings, pelvic computed tomography, magnetic resonance image and radio-nucleotide bone scans, the tumor stage was determined using tumor-node-metastasis (TNM) classification and graded according to WHO guidelines; pathologic grade was recorded as the Gleason score.

2.2 Genotyping

Polymorphisms were analyzed by polymorphism chain reaction and ligase detection reaction (PCR-LDR). Each PCR reaction was done in a total volume of 15 ul, which contains 1 ul genomic DNA, 2.5 pmol of each promer, 10× buffer 1.5 ul, $MgCl_2$ 1.5 ul, 0.3 ul of dNTP (MBI, Inc.), 0.25 ul of Taq DNA Polymerase (MBI, Inc.) and ddH_2O 9.95 ul. PCR was subjected to 35 thermal cycles at 94°C 15 sec, 56°C for 15 sec, and 72°C for 60 sec conducted on the ABI 9600 (ABI, Inc.). Primers were 5′-TGACGACTTCTTCCTCTTTGC-3′ (sense) 5′-GATAGTGACAGCGAGACATTG-3′ (antisense). The probes for LDR were: 5′-P-GTAGGAAGTAGTTGACACACTCAGATTT-FAM-3′ with common phosphorylated 5′-end and 6-carboxy X-uorescein (FAM) labeled 3′-end, the A-specific probe 5′ TTTTCATGCCTGTGTGTTAGGCTGCACAA-3′, the G-specific probe 5′-ttttTTCATGCCTGTGTGTTAGGCTGCACAG-3′. For each PCR product, the ligation reaction was performed in a final volume of 10 ul, which contains 3 ul PCR product, 10×Taq DNA ligase buffer 1 ul, 5 U of Taq DNA ligase (NEB, Inc.,), 0.1 pmol of each probe, and ddH_2O 5.575 ul. The LDR parameters were as follows: 25 thermal cycles at 94 °C for 30 sec and 60°C for 30 min. The LDR reaction products were analyzed on ABI 3730 DNA Sequencer (ABI, Inc.,). To confirm the accuracy of PCR-LDR genotyping method, direct DNA sequencing of randomly selected PCR products was performed. The proportion of the sequencing samples were about 5%, the results of the PCR-LDR genotyping showed 100% concordance to direct DNA sequencing of the randomly selected PCR products.

2.3 Enzyme-linked immunosorbent assay (ELISA)

Blood was collected in standard cubes without anticoagulant and was immediately centrifuged for 20 min, at 3,000 rpm. Serums were stored at -808°C until serum TRAIL levels were measured by ELISA kit (R&D Systems, Inc.). The optical density was determined by measuring the absorbance at 450 nm. The absorbance was correlated against a standard curve.

2.4 Statistical analysis

Hardy–Weinberg equilibrium (HWE) was tested among controls using the Pearson chi-square test. Differences in the distributions of demographic characteristics, selected variables and frequencies of genotypes of TRAIL -716 A>G polymorphism between the cases and controls were evaluated by using the student's t-test (for continuous variables) or chi-square (χ^2) test (for categorical variables). The odds ratios (OR) and 95% confidence internals (CI) were calculated by logistic regression analysis to quantify the association between TRAIL -716 A>G polymorphism and risk of PCa with the adjustment for potential covariates (age, BMI, cigarette smoking, alcohol drinking and family history of cancers). The correlation between the serum TRAIL levels and genotypes of TRAIL -716 A>G polymorphism were evaluated by one-way ANOVA. A *P*-value < 0.05 was considered statistically significant and all statistical tests were two sided. All statistical analyses were performed with Statistics Analysis System software (Version 9.1.3; SAS Institute, Inc., Cary, NC).

3. Results

3.1 Characteristics of the study population

One hundred and eighty-seven patients and 237 cancer-free controls were enrolled in our study. The distribution of relevant demographic and clinical characteristics is presented in Table 1. Baseline characteristics were similar between cases and controls, except that the frequency of relatives with cancer from the case group was higher, compared to non-relatives (27.27% vs. 15.61%, $P = 0.003$); there were more subjects who had larger body mass index (>23 kg/m^2) among the cases than among the controls (60.43% vs. 50.21%, $P = 0.036$), the frequency of ever alcohol drinking in cases was higher than in controls (34.22% vs. 20.68%, $P = 0.002$) and the mean ± SD PSA levels of PCa patients and control subjects were 80.45 ± 262.25 and 2.14 ± 1.42 ng/ml, respectively ($P < 0.001$).

Characteristics	Csaes (n=187)		Controls (n=237)		*P*-Value
	n	%	n	%	
Age (year)					0.687
≤70	55	29.41	74	31.22	
＞70	132	70.59	163	68.78	
BMI (kg/m2)					0.036
≤23	74	39.57	118	49.79	
＞23	113	60.43	119	50.21	
Cigarette smoking					0.839
Never	81	43.32	105	44.30	
Ever	106	56.68	132	55.70	
Alcohol drinking					0.002
Never	123	65.78	188	79.32	
Ever	64	34.22	49	20.68	
Family history of cancers					0.003
No	136	72.73	200	84.39	
Yes	51	27.27	37	15.61	
PSA(ng/ml)					
Mean ± SD	80.45	±262.25	2.14	±1.42	＜0.001
Clinical stage					
Localized	86	46.00			
Advanced	101	54.00			
Gleason score					
＜7	50	26.74			
= 7	70	37.43			
＞7	67	35.82			

BMI: body mass index

Table 1. Demographic characteristic of PCa cases and controls

3.2 Genotype distributions of TRAIL -716 A>G polymorphism and risk of PCa

The distribution of TRAIL -716 A>G in the control group was 21.10% for AA homozygote, 51.48% for AG heterozygote, 27.42% for GG homozygote, and was in Hardy–Weinberg equilibrium ($\chi^2 = 0.268$, $P = 0.604$). As shown in Table 2, the TRAIL -716 A>G polymorphism

was not associated with total PCa. After adjusting for potential covariates (age, BMI, cigarette smoking, alcohol drinking, family history of cancers), compared with AA homozygote, subjects carrying GG homozygote did not have any association between cases and controls (OR = 0.94, 95%CI = 0.69-1.27, *P* = 0.397). In addition, no association was also found between subjects carrying AG/GG genotypes and AA homozygote (OR = 0.87, 95%CI = 0.54-1.41, *P* = 0.577).

Genotype	PCa, No. (%)	Controls[a], No. (%)	*P*-value[b]	Adjusted OR(95%CI)[c]
Total	187	237		
AA	44(23.53)	50(21.10)		1.00(reference)
AG	98(52.41)	122(51.48)	0.712	0.89(0.54-1.47)
GG	45(24.06)	65(27.42)	0.397	0.94(0.69-1.27)
AA	44(23.53)	50(21.10)		1.00(reference)
AG+GG	143(76.47)	187(78.90)	0.577	0.87(0.54-1.41)

[a]The genotype frequencies among the control subjects were in agreement with the Hardy-Weinberg equilibrium ($\chi 2 = 0.268$, P = 0.604).
[b]Two-sided $\chi 2$ test for the distributions of genotypes frequencies between the cases and controls.
[c]Odd ratios (ORs) were obtained from a logistic regression model with adjusting for age, BMI, cigarette smoking, alcohol drinking, family history of cancers; 95%CI, 95% confidence interval.

Table 2. Genotypes in patients with PCa and controls

3.3 Stratified analysis

The association between genotypes and PCa risk stratified by disease stage (Localized: $T_{1\text{-}2}N_0M_0$; Advanced: $T_{3\text{-}4}N_XM_X$ or $T_XN_1M_X$ or $T_XN_XM_1$), pathologic grade (Gleason score < 7, = 7 and >7) and serum PSA level (≤ 20 and >20) is shown in Table 3. These associations were in the same direction for advanced, higher grade disease and PSA level but were not statistically significant.

Variables	TRAIL-716A/G		*P*-value[a]	Adjusted OR (95% CI)[b]
	AA,No.(%)	AG/GG,No.(%)		
Control	50(21.10)	187(78.90)		1.00(reference)
Clinical stage[c]				
Localized	15(17.65)	70(82.35)	0.644	1.17(0.60-2.27)
Advanced	29(28.43)	73(71.57)	0.158	0.67(0.38-1.17)
Gleason score				
<7	6(12.00)	44(88.00)	0.117	2.14(0.83-5.53)
= 7	19(27.14)	51(72.86)	0.226	0.68(0.36-1.27)
>7	19(28.36)	48(71.64)	0.117	0.59(0.31-1.14)
PSA				
≤ 20	16(17.58)	75(82.42)	0.626	1.17(0.62-2.23)
>20	28(28.87)	69(71.13)	0.121	0.64(0.36-1.13)

[a]Two-sided $\chi 2$ test for the distributions of genotypes frequencies between the cases and controls.
[b]Odd ratios (ORs) were obtained from a logistic regression model with adjusting for age, BMI, cigarette smoking, alcohol drinking, family history of cancers; 95%CI, 95% confidence interval.
[c]Localized: T1-2N0M0; Advanced: T3-4NXMX or TXN1MX or TXNXM1 [according to the international tumor-node-metastasis (TNM) staging system for PCa].

Table 3. TRAIL-716A/G and clinico-pathological characteristics in patients with PCa

In addition, as show in Table 4, the association between TRAIL -716 A>G polymorphism and PCa did not vary by cigarette smoking and alcohol drinking. However, the association appeared stronger in subgroups of BMI >23kg/m^2 (OR = 0.58, 95%CI = 0.31-0.89), age ≤70 years (OR = 0.32, 95%CI = 0.12-0.87) and no family history of cancers (OR = 0.86, 95%CI = 0.51-0.96).

Variables	N (case/control)	Genotypes(case/control)				*P*-value[a]	Adjusted OR(95%CI) [b]
		AA genotype		AG/GG genotype			
		n	%	n	%		
Total	187/237	44/50	23.53/21.10	143/187	76.47/78.90	0.577	0.87 (0.54-1.41)
Age(years)							
≤ 70	55/74	13/9	23.64/12.16	42/65	76.36/87.84	0.026	0.32 (0.12-0.87)
>70	132/163	31/41	23.48/25.15	101/122	76.52/74.85	0.575	1.17 (0.67-2.04)
BMI (kg/m2)							
≤ 23	74/118	12/27	16.22/22.88	62/91	83.78/77.12	0.165	1.78 (0.79-3.99)
>23	113/119	32/23	28.32/19.33	81/96	71.68/80.67	0.042	0.58 (0.31-0.89)
Cigarette smoking							
Never	81/105	20/26	24.69/24.76	61/79	75.31/75.24	0.967	0.99 (0.49-1.97)
Ever	106/132	24/24	22.64/18.18	82/108	77.36/81.82	0.535	0.81 (0.41-1.58)
Alcohol drinking							
Never	123/188	29/39	23.58/20.74	94/149	76.42/79.26	0.513	0.83 (0.48-1.45)
Ever	64/49	15/11	23.44/22.45	49/38	76.56/77.55	0.944	0.97 (0.38-2.45)
Family history of cancers							
No	136/200	34/44	25.00/22.00	102/156	75.00/78.00	0.034	0.86 (0.51-0.96)
Yes	51/37	10/6	19.61/16.22	41/31	80.39/83.78	0.972	1.02 (0.31-3.32)

[a]Two-sided $\chi 2$ test for the distributions of genotypes frequencies between the cases and controls.
[b]Odd ratios (ORs) were obtained from a logistic regression model with adjusting for age, BMI, cigarette smoking, alcohol drinking, family history of cancers; 95%CI, 95% confidence interval. BMI: body mass index.

Table 4. Association and stratification between TRAIL-716A/G and PCa risk.

3.4 Association of TRAIL -716 A>G polymorphism with expression levels of TRAIL

We collected 83 tumor serum samples obtained from in present study with different genotypes of the TRAIL -716 A>G polymorphism, and the distribution of the AA, AG, and

GG genotypes was 27 (32.53%), 44 (53.01%) and 12 (14.46%), respectively. Moreover, serum TRAIL levels in PCa patients with AG/GG genotypes were significantly higher than those with AA genotypes (901.18 ± 189.58 μg/L vs. 819.13 ± 111.00 μg/L, $P = 0.041$; Fig. 2)

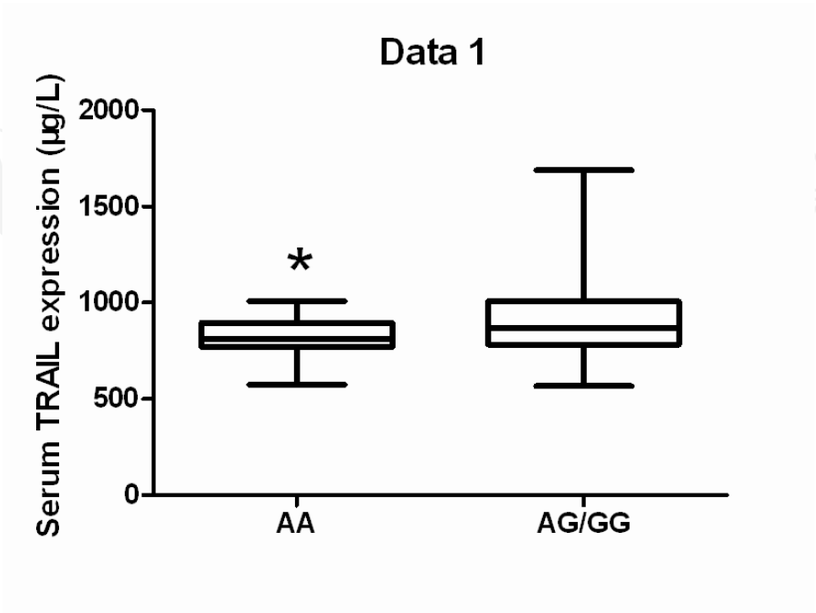

Fig. 2. Analysis of serum TRAIL levels in three groups of PCa cases with mean values (horizontal lines, mean values). * $P = 0.041$ compared with the AG/GG and AA genotypes.

4. Discussion

Recently, Kuribayashi et al. [23] indicated a direct regulation of TRAIL gene by p53 protein. Moreover, early growth response protein (EGR) [24], interferon regulatory factor 1 (IRF1) [25], NF-$_k$B [26], SP1 [27] and PU1 [28] have been implicated in the regulation of TRAIL. TRAIL is present in various tissues, particular in the prostate, spleen and lung.

TRAIL binds to two different types of receptors: death receptors and decoy receptors. TRAIL can also bind to osteoprotegerin (OPG) (a soluble inhibitor of receptor activator of NF-$_k$B ligand) at low affinity. To date, four human receptors specific for TRAIL have been recognized: the death receptors TRAIL-R1 (also know as DR4), TRAIL-R2 (also known as DR5), the putative decoy receptors TRAIL-R3 (DcR1) and TRAIL-R4 (DcR2). TRAIL-R1 (DR4) is expressed at very low levels in most human tissues including the spleen, thymus, liver, peripheral blood leukocytes, activated T cells, small intestine and some tumor cell lines. TRAIL-R2 (DR5) is ubiquitiously distributed both in normal and tumor cell lines but is more abundant in spleen, peripheral blood leukocytes, activated lymphocytes and hepatocyes [29-31].

TRAIL has attained the centre stage in anti-tumor drug discovery because of its efficacy in killing tumor cells without lethal toxicity in pre-clinical models apart from the inherent property to activate both the extrinsic and intrinsic apoptotic pathways [32-34].

Single nucleotide polymorphisms (SNPs) are the most abundant form of genetic variation in the human genome. By convention, a point mutation is referred to as a SNP when the frequency of the minor (rarer) allele exceeds 1% in at least one population. For example, a

SNP in a regulatory region may have an influence on gene transcription, a SNP located in a RNA splice site may affect RNA splicing, a SNP in the 3'-untranslated region of a gene may have an effect on mRNA stability, and a SNP in the coding region may result in an amino acid substitution in the encoded protein. It is thought that SNPs contribute to interindividual variability in susceptibility to common diseases such as cancer [35, 36].

So far, some published meta-analyses have confirmed that a number of SNPs are associated with increased or decreased PCa risk in different races, such as A49T in steroid-5-alpha-reductase, alpha polypeptide 2 (SRD5A2) gene [37], Gly388Arg in fibroblast growth factor receptor 4 (FGFR4) gene [38], -160C/A in E-cadherin (CDH1) gene [39], Val16Ala in manganese superoxide dismutase (MnSOD) gene [40], C677T in 5,10-methylenetetrahydrofolate reductase (MTHFR) gene [41].

Several studies have investigated the possible role of anti-tumor gene polymorphisms and the prevalence of PCa. This impairment of host factors might result in susceptibility or resistance to tumor progression. The transcription factor Sp3 (stimulatory protein 3) exhibits a similar DNA binding affinity for Sp1 consensus sequence [42-44] and represses the Sp1-mediated trans-activation of promoters with two or more Sp1 sites [45-47]. TRAIL has two Sp1 consensus sequences in the basal promoter [48, 49]. AA genotype at -716 in TRAIL promoter with additional Sp1 consensus sequence can decrease TRAIL expression due to the repression caused by binding of Sp3, whereas, GG genotype background at the same position can increase TRAIL expression because of the lower probability of Sp3 driven repression. To date, only one study [22] showed the association between TRAIL -716 A>G polymorphism and cancer risk: individuals with -716 GG genotype were at a greater risk of developing breast cancer, in addition, G allele resulted in a higher expression than the A allele to regulate the expression of TRAIL in four different cancer cell lines (HeLa, MCF-7, HepG2, HT1080).

To the best of our knowledge this is the first study investigating the genetic association of polymorphism of the -716 site in TRAIL gene with PCa and the expression of TRAIL with different genotypes in serum of cases in southern Chinese Han descent. No statistically significant association was observed between TRAIL -716 A>G polymorphism and PCa. Moreover, when stratifying the case group by clinical characteristics, the present study also did not find any association among PSA, Gleason and clinical stage. There must be some factors that would contribute to this discrepancy. First, TRAIL -716 A>G polymorphism might play a different role in different cancers. Second, multiple genes and environmental factors may lead to cancer formation. Third, race may be related to cancer. Either through common risk factors or other genes in linkage disequilibrium with TRAIL suggests that a possible role of ethnic differences is in genetic backgrounds and the environment they lived in.

Furthermore, we found that the decreased risk associated with the AG/GG genotypes was more pronounced in: subjects with age ≤70 years (OR = 0.32, 95%CI = 0.12-0.87) and no family history of cancers (OR = 0.86, 95%CI = 0.51-0.96). It confirmed the concept that younger age and no family history of cancers might be protective factors for PCa. In addition, we found that the OR for AG/GG genotypes was 0.58(95%CI = 0.31-0.89) among subjects with BMI >23kg/m^2. This finding may reflect that PCa formation may be subject to a variety of environmental and genetic factors. In these subgroups, other high level of genetic susceptibilities or other unknown risk factors may influence our results.

Except for above associated results, we detected the expression of TRAIL in the serums of the cases. We found that the protective genotypes AG/GG were associated with higher

serum TRAIL expression when compared with the AA genotype. Previous one study [22] have reported that the G allele resulted in a higher expression than the A allele. Our work confirmed the findings of this study. Furthermore, since TRAIL can be measured in the blood and the serum level has been found significantly different in different genotypes in PCa cases, this may be a novel tumor marker and provide a future screening target. We need further investigations on the molecular mechanisms of how genetic variants might affect the TRAIL expression.

This study has several potential limitations. First of all, it is well known that sporadic and familial PCa have frequently quite different epidemiological and molecular peculiarities, clinical evolution and prognosis, so it is better to analysis these two kinds of PCa, respectively, however, we got together as a whole case group. Second, the numbers of cases/controls in our studies were not sufficiently large for a comprehensive analysis. Third, the control group in our study contained not only the healthy old matched man but also the benign prostatic hyperplasia (BPH), which was not the strict 'control'.

5. Conclusions

Our study suggested that a functional polymorphism -716 A>G in the TRAIL gene may play a role in the development of PCa in southern Chinese Han descent, and the protective genotypes AG/GG of -716 A>G were associated with increased TRAIL expression in serum, which makes it a potential role in early detection for PCa. Moreover, further investigations with larger sample size are needed to confirm this relationship and to elucidate the mechanism responsible for this association.

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7. Conflict of interest

The authors declare that they have no conflict of interest related to the publication of this manuscript.

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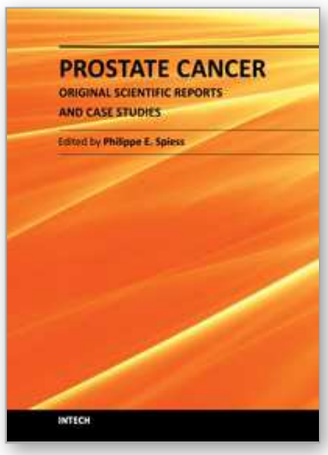

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This book encompasses three sections pertaining to the topics of cancer biology, diagnostic markers, and therapeutic novelties. It represents an essential resource for healthcare professionals and scientist dedicated to the field of prostate cancer research. This book is a celebration of the significant advances made within this field over the past decade, with the hopes that this is the stepping stone for the eradication of this potentially debilitating and/or fatal malignancy.

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