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ORIGINAL PAPER

Polymorphisms of peroxiredoxin 1, 2 and 6 are not associated with esophageal cancer

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Abstract
Purpose Peroxiredoxins, which reduced intracellular peroxides as a noval kind of antioxidant protein, were extensively expressed in various types of cancers and were thought as a biomarker of cancer cells. In this work, we performed genotyping analyses for tag SNP of Prdx 1, 2 and 6, and then evaluated the association with susceptibility and clinic stage of esophageal squamous cell carcinoma (ESCC) in a case–control study.
Methods The protein level of these Prdx isoforms in ESCC cancer samples was evaluated by Western blot. Then 356 ESCC cancer cases and 315 controls were genotyped by SNPshot assay. Differences in frequencies of the genotypes of the SNPs variant between the cases and controls were evaluated by using the chi-square test.
Results Our result of Western blot confirmed the aberrant expression of Prdx 1, 2 and 6 in ESCC samples, which was coincident with other studies. After genotyping by SNPshot assay, the result showed that the allele and genotype frequencies did not differ between the patients and controls. And no association between the polymorphism and the progression of ESCC including tumor grade and stage was found.
Conclusions Our data suggested that polymorphisms of Prdx 1, 2 and 6 were not associated with esophageal cancer.

Keywords Peroxiredoxin · Esophageal cancer · Polymorphisms

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Introduction

Esophageal cancer, including esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma, is one of the leading causes of cancer-related death, and its incidence was increasing year by year in the world (Schuchert et al. 2010). According to a review, Taihang Mountain region in northern China has the highest incidence of ESCC in the world, with an incidence rate of approximately 150 per 100,000 population (Yang 1980). Despite attempts to improve outcomes with aggressive multimodality therapy, prognosis remains poor with a 5-year overall survival of 16% (Lagarde et al. 2006). Studies of identification of molecular prognostic markers for esophageal cancer are the hotspot in this field, which will enable the personalized treatment of cancer patients in the future.

The process of tumorigenesis is accompanied by cumulative mutations in genetic pathways that confer a growth advantage of cancer. So this process is thought to be involved with many genes (e.g. oncogenes and tumor suppressors) and is a result of multistage of mutagenesis. As for other environmental factors associated with tumorigenesis, reactive oxygen species (ROS) was one of the most important factors attracting researchers' interest. Disturbance of the balance between ROS and the antioxidant defense mechanisms are thought to be important in carcinogenesis and the responses to anticancer treatment (Ziech et al. 2011). As ROS could lead to damages of DNA, antioxidant enzymes could counteract ROS and help to keep the stability of genome. Thus, antioxidant enzymes are associated with tumorigenesis.

Peroxiredoxins (Prdxs), a family of peroxidase that reduced intracellular peroxides with the thioredoxin system as the electron donor, were highly expressed in various cellular compartments. The function of this gene family included reduction of ROS by thioredoxin peroxidase, protecting

against free radical-sensitive proteins involved in cell proliferation and differentiation and signal transduction (Kang et al. 2005; Wang et al. 2010a, b; Woo et al. 2010). In mammals, the gene family consists of six isoforms, which divided into 1-Cys and 2-Cys Prdx subfamily according to its conserved cysteine. Many studies indicated that aberrant expression of Prdx was found in various kinds of cancers (Zhang et al. 2009a). For example, it was reported that Prdx 1 was significantly associated with the tumor burden, and Prdx 1 positivity was linked to a poor response to neoadjuvant therapy and worse survival (Chen et al. 2010). By using immunohistochemical staining, it was found that Prdx 1 expression is an important factor in esophageal squamous cancer progression and could serve as a useful prognostic marker (Hoshino et al. 2007). Besides Prdx 1, other isoforms of this gene family were also found to be associated with cancers by gene expression analysis. Moreover, some members of Prdxs were thought to be a biomarker of cancer cells. All these studies were interested in gene expression at protein or mRNA level (Zhang, et al. 2009b; Kim et al. 2009). However, whether the genetic polymorphism of Prdx family is associated with cancer onset is still unknown. In this work, we performed genotyping analyses for tag SNP of Prdx 1, 2 and 6, and then evaluated the association with susceptibility and clinic stage of ESCC in a case–control study in a Chinese Han population.

Materials and methods

Study populations

The hospital-based case–control study has been described previously (Xiong et al. 2010; Wang et al. 2010a, b) and approved by the institutional review board of Third Military Medical University. The ESCC patients were histopathologically diagnosed and recruited between July 2005 and August 2009 at the Southwest Hospital (Chongqing, China), without the restrictions of age and sex. The exclusion criteria included previous cancer, metastasized cancer and family history of cancer. Cancer-free controls, having no history or family history of cancer and other genetic disease, were recruited from individuals who visited the same hospital for physical examination between 2005 and 2009 and were frequency matched to the cases on age, gender and residential area (urban or countryside). Totally, 356 incident ESCC cancer cases and 315 controls were genotyped in the current study. All the participants were genetically unrelated, ethnic Han Chinese.

Western blot

ESCC tissues and paired adjacent esophageal tissue (at least 5 cm distal from primary tumor mass) were obtained during surgical resection. After excision, sample tissues were frozen immediately at −80° and stored until use. Total proteins, isolated from cancer and adjacent normal tissues using RIPA buffer, were separated on 12% SDS–polyacrylamide gel and transferred to nitrocellulose membranes. After being blocked for 1 h with the Tris/NaCl containing 5% milk powder, the membranes were probed with specific antibodies against Prdx 1, 2, 6 (Abfrontier, Seoul, Korrea) and GAPDH (Kangcheng Corp., Shanghai, China). Following washing, the blots were incubated for 2 h with horseradish peroxidase-labeled anti-goat/rabbit IgG (Zhongshan Corp., Beijing, China). The band of each protein was visualized by using the enhanced chemiluminescence system (Pierce, Rockford, IL, USA). The protein expression of each sample was normalized by that of GAPDH with Quantity One software.

DNA isolation

Genomic DNA was isolated from fresh blood by using Wizard Genomic DNA PuriWcation Kit (Promega, USA) according to the manufacturer's protocol. The quantity and quality of DNA was determined by using NANODROP 1000 (Theremo, USA).

Genotyping assays

All tag SNPs, which covered most blocks of these genes, were selected based on the data from hapmap.com. SNPshot assay was performed to genotype the SNPs. Firstly, the specific DNA fragment spanning each SNP of interest was amplified by using regular PCR, which was carried out in a total volume of 20 μl containing 0.2 μg genomic DNA, 0.5 pmol of each primer and 10 μl master mix (Tiangen, China). Primers for each Tag SNP of Prdx 1, 2 and 6 were listed in Table 1. After purification by using FastAP Thermosensitive Alkaline Phosphatase and Exonuclease I (Fermentas, USA), the PCR products were mixed and used as template in the SNPshot PCR. The SNPshot PCR was run in a 10 μl volume containing 3 μl mixed PCR products, 5 μl SNPshot multiplex kit (ABI, USA), 1 μl mixed primers and 1 μl water. The PCR condition contained 25 cycles of 10 s at 96°C, 5 s at 50°C and 30 s at 60°C. Then, the reaction product was purified by adding 1U FastAP Thermosensitive Alkaline Phosphatase (Fermentas, USA) for 1 h at 37°C and diluted in Hi-Di Formamide (ABI, USA) with Liz120 (ABI, USA). Electrophoresis was carried out on the ABI 3130 Genetic Analyzer (ABI), and the data was analyzed by the software Genescan 4.0 (ABI). Ten percent of the samples were randomly selected for repeated assays.

Statistical analyses

Hardy–Weinberg equilibrium was tested by a chi-square test to compare the observed genotype frequencies to the

Table 1 Primers for genomic PCR and SNPshot PCR

Gene name	Tag SNP	Genomic PCR primer	SNPshot primer[a]
Prdx 1	rs713358	F: GGCGACAGGGTGAGTGAGACT R: CAGGGTTGCTGCTTTCTGTTGTA	GTGTATGTGTGTTTGTGGGG
	rs4633317	F: CCCAAGAGCGAAACTCCGTCAAA R: TCCAAATGCACAATGCCACAAAC	T(52)-GAAGGCAGGTGGAGGCAC
	rs11211129	F: AGTTCTGGGATTACAGGCGTGAG R: AACCCTTCCAGCTTTGCCTAACA	T(11)-AGTTCCAGAGCAGCTCGATCTCCT
Prdx 2	rs1205171	F: AACATTGCCGCCCAAGTCTTTAA R: CACGCCGTAATCCTCAGACAAGC	T(17)-CTGGGTGATGCTGCAAGTTACAAG
	rs12151144	F: GTCTTGGTTCGGGCCGGGCATAA R: CGACAGCACTAACCCTCACCCTC	T(47)-ACAGCCTTGCAGCGCAGGCC
Prdx 6	rs7540065	F: GGGAAGGACGTGAACTGGCTTAA R: ACGGCTGCCACTCAACTCCCAAG	T(30)-AACAGTCTTTATGGACTCACA
	rs912767	F: TTGCCCTCATAGAACTTCCATTC R: CTTTCCTTGTATTCCTCCAACAT	T(37)-ATACTTGTGAGGGACGAGCACTAT
	rs7314	F: TTTAACTGTCCTATCACGTCCTC R: AAATAGCAACCCACTGCAAGA	T(21)-CTTCACTTATCTACTAGGAAGGTA

[a] Oligo-dT was added to specific sequence of each target

expected ones. Differences in frequencies of the genotypes of the SNPs variant between the cases and controls were evaluated by using the chi-square test. The associations between each SNP genotype and the risk of esophageal cancer were estimated by computing the odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analyses with the adjustment for age. All of the statistical analyses were performed with Statistical Analysis System software (9.1.3; SAS Institute, USA).

Result and discussion

The aberrant expression of Prdx family was observed in various types of cancer. The expression of Prdx 1 in cancer cells has been most extensively studied (Zhang et al. 2009a; Neumann and Fang 2007). Compared with its expression in normal tissues, Prdx 1 expression was augmented in many kinds of cancer types including thyroid, lung, breast and esophageal carcinoma. Prdx 2 was the most homologous molecule of Prdx 1 and showed similar cellular localization. Although human Prdx 1 and 2 are more than 90% homologous in their amino acid sequences, they are not duplicate proteins (Lee et al. 2007). Similar with Prdx 1 isoform, the increased expression of Prdx 2 was observed in lung, breast and hepatocellular carcinomas. Prdx 6 has also been shown to be protective against oxidant stress, which null models show sensitivity to oxidants. A recent study demonstrated that Prdx 6 promoted lung cancer metastasis and invasion via phospholipase A2 activity in mice (Ho et al. 2010). In order to confirm the expression of

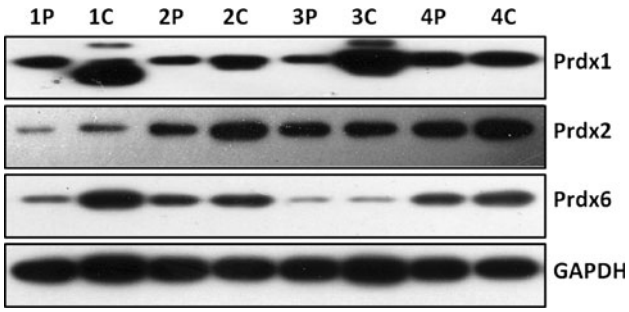

Fig. 1 Western blotting. Total proteins of cancer and adjacent tissues were isolated and separated on 12% SDS–PAGE gel. After transferring and blocking, the membranes were incubated with antibodies and then visualized by using the enhanced chemiluminescence system. *C* cancer tissues, *P* adjacent tissues

Prdx isoforms in ESCC samples, the protein levels in random selected tissue pairs of cancer and adjacent tissue were detected by Western blot. Increased expression of all three isoforms was observed in most samples, which was consistent with other studies (Fig. 1).

As the expression of Prdx 1, 2 and 6 was increased in cancer tissues, we wondered whether the polymorphism of these isoforms was associated with tumorigenesis of ESCC. Thus, SNP analysis of ESCC cases and controls was performed in this study. Our study was comprised of 356 esophageal cancer patients (205 men and 141 women), and 315 healthy controls. The characteristics of these subjects were summarized in Table 2. There were no statistically significant differences between cases and controls in terms of the frequency distribution of sex and age. Most of the ESCC cases were well or moderate differentiated.

For SNPshot assay of each sample, we designed an octuple detection of the tag SNPs of interest. A typical detection of these samples was shown in Fig. 2. Although this method is consistent and easy to use, its overall accuracy is lower than other methods such as Pyrosequencing and Biplex Invader (Pati et al. 2004). Thus, we chose 10% of the samples for repeated assays, and the results were 100% concordant in our system.

All SNPs were in Hardy–Weinberg equilibrium except rs4633317, both in the patient and in the control group. Maybe this disequilibrium was relative to sample size, or it represented a recent mutation in this population. However, the allele and genotype frequencies did not differ between the patients and controls for all 8 SNPs, indicating that there is no significant association between the polymorphisms of Prdx isoforms and the risk of ESCC cancer (Table 3). We also analyzed the polymorphisms of these Prdx isoforms and clinicopathological characteristics, and the result showed no association between the polymorphism and the progression of ESCC including tumor grade and stage (Table 4).

Table 2 General characteristics of the subjects

	ESCC patients	Controls	*P*
Total	356	315	
Age (years)	58.2 ± 8.1	56.4 ± 7.7	>0.05
Sex			>0.05
Men	205	172	
Women	151	143	
Tumor grade			
Well	172 (48.3)		
Moderate	135 (37.9%)		
Poor	49 (13.8%)		
TMM stage			
I	16 (4.5%)		
IIa	206 (57.9%)		
IIb	83 (23.3)		
III	32 (9.0%)		
IV	19 (5.3%)		

To date, there is no report about the association between Prdxs polymorphisms and the risk of cancer. However, polymorphisms of some Prdxs isoforms were found to be associated with other diseases or traits. It was reported that two intronic Prdx 2 SNPs probably had a more efficient reduction of arsenic metabolism in indigenous women from northern Argentina (Schläwicke Engström et al. 2009). Rushefski et al. (2011) analyzed the SNPs of Prdx 6 for its association with acute lung injury, and their results showed no significant association. In this work, we failed to find any association of polymorphism with the risk of ESCC cancer. This lack of association may be due to several causes. The first reason might be the sample size. Totally, 671 subjects were genotyped to test for an association. Theoretically, this sample size was inadequate to detect relative risks below 1.5 for alleles with MAFs of 0.20 (Haubold and Wiehe 2003). More samples are needed for lower relative risk and MAF. Second, it is possible that the genetic variations of Prdx isoforms may not modify the risk of ESCC cancer. Finally, it might be the ethnic reason. All our subjects were ethnic Han Chinese. As it is reported, some polymorphisms associated with a disease or trait in one population was not associated with the same disease in another population (Li et al. 2011; Wei et al. 2011).

As mentioned above, aberrant expression of Prdx isoforms was found in various types of cancer including ESCC cancer, and our data indicated that these polymorphisms of

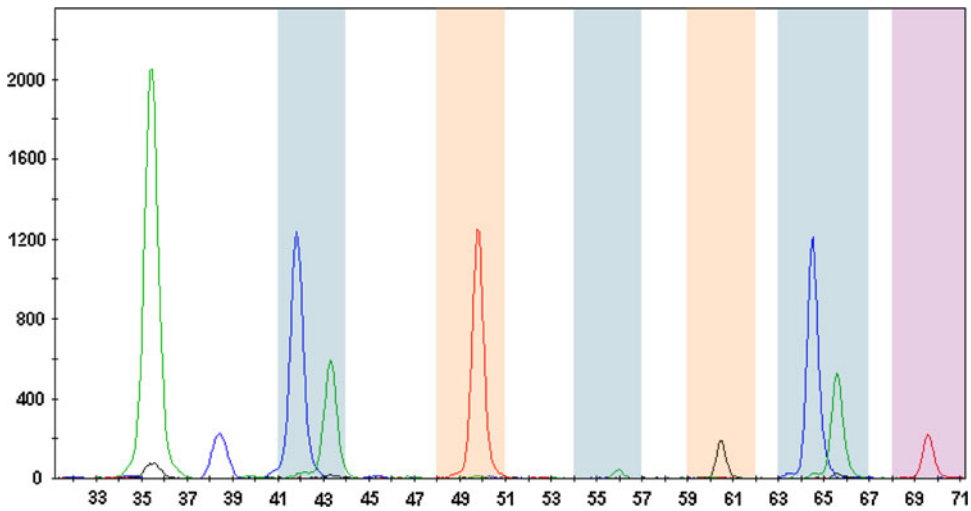

Fig. 2 A typical detection by SNPshot assay. Electrophoresis of SNPshot PCR product was carried out on the ABI 3130 Genetic Analyzer, and the data was thus analyzed

Table 3 Genotype and allelic frequencies of SNP polymorphism in cases and controls

SNP	Types	ESCC cases	Controls	Odds ratio	*P* value
rs11211129	GG	48 (17.5%)	42 (14.8%)	1 (Reference)	–
	GA	125 (45.6%)	140 (49.5%)	0.78 (0.48–1.26)	0.31
	AA	101 (36.9%)	101 (35.7)	1 (0.615–1.626)	1.00
	G	221 (40.3%)	224 (39.6%)	1 (Reference)	–
	A	327 (59.7%)	342 (60.4%)	0.97 (0.76–1.23)	0.80
rs713358	CC	10 (3.0%)	12 (4.1%)	1 (Reference)	–
	CG	128 (38.3%)	117 (40.1%)	1.31 (0.55–3.15)	0.54
	GG	196 (58.7%)	163 (55.8%)	1.44 (0.61–3.42)	0.40
	C	148 (22.2%)	141 (24.1%)	1 (Reference)	–
	G	520 (77.8%)	443 (75.9%)	1.11 (0.90–1.37)	0.31
rs4633317	AA	102 (29.7%)	99 (32.9%)	1 (Reference)	–
	AG	224 (65.3%)	193 (64.1%)	1.13 (0.80–1.58)	0.49
	GG	17 (5.0%)	9 (3.0)	1.83 (0.78–4.31)	0.16
	A	428 (62.4%)	391 (65.0%)	1 (Reference)	–
	G	258 (37.6%)	211 (35.0%)	1.12 (0.93–1.34)	0.23
rs1205171	CC	57 (17.1%)	53 (18.0%)	1 (Reference)	–
	CT	158 (47.5%)	153 (51.8%)	0.96 (0.62–1.48)	0.85
	TT	118 (35.4%)	89 (30.2%)	1.23 (0.77–1.96)	0.38
	C	272 (40.8%)	259 (43.9%)	1 (Reference)	–
	T	394 (59.2%)	331 (56.1%)	1.13 (0.95–1.36)	0.16
rs12151144	CC	203 (59.4%)	190 (63.6%)	1 (Reference)	–
	CT	120 (35.1%)	97 (32.4%)	1.16 (0.83–1.61)	0.39
	TT	19 (5.5%)	12 (4.0%)	1.48 (0.70–3.13)	0.30
	C	526 (76.9%)	477 (79.8%)	1 (Reference)	–
	T	158 (23.1%)	121 (20.2%)	1.19 (0.96–1.47)	0.11
rs7540065	AA	44 (14.7%)	50 (17.4%)	1 (Reference)	–
	AG	142 (47.3%)	141 (48.9%)	1.14 (0.72–1.83)	0.57
	GG	114 (38.0%)	97 (33.7%)	1.34 (0.82–2.17)	0.24
	A	230 (38.3%)	241 (41.8%)	1 (Reference)	–
	G	370 (61.7%)	335 (58.2%)	1.16 (0.97–1.38)	0.11
rs912767	AA	143 (41.0%)	111 (36.3%)	1 (Reference)	–
	AG	170 (48.7%)	157 (51.3%)	0.84 (0.60–1.17)	0.30
	GG	36 (10.3%)	38 (12.4%)	0.73 (0.44–1.24)	0.24
	A	456 (65.3%)	379 (61.9%)	1 (Reference)	–
	G	242 (34.7%)	233 (38.1%)	0.86 (0.72–1.04)	0.11
rs7314	CC	67 (22.1%)	65 (22.4%)	1 (Reference)	–
	CT	144 (47.5%)	147 (50.7%)	0.95 (0.63–1.43)	0.81
	TT	92 (30.4%)	78 (26.9%)	1.14 (0.73–1.80)	0.56
	C	278 (45.9%)	277 (47.8%)	1 (Reference)	–
	T	328 (54.1%)	303 (52.2%)	1.08 (0.9–1.29)	0.39

Prdx isoforms did not contribute to the risk of ESCC cancer in a Chinese population. We supposed that the gene regulation of Prdx isoforms was more important at transcriptional level than at DNA level.

Table 4 Stratification analyses of genotype and allelic frequencies in ESCC patients according to TNM stage

SNP	Types	TMM stage		
		I–IIa	IIb–IV	*P* value
rs11211129	GG	31 (17.8%)	17 (17.0%)	–
	GA	79 (45.4%)	46 (46.0%)	0.87
	AA	64 (36.8%)	37 (37.0%)	0.88
	G	141 (40.5%)	80 (40.0%)	–
	A	207 (59.5%)	120 (60.0%)	0.90
rs713358	CC	6 (2.7%)	4 (3.5%)	–
	CG	81 (37.2%)	47 (40.5%)	0.84
	GG	131 (60.1%	65 (56.0%)	0.65
	C	93 (21.3%)	55 (23.7%)	–
	G	343 (78.7%)	177 (76.3%)	0.48
rs4633317	AA	64 (29.5%)	38 (30.1%)	–
	AG	142 (65.4%)	82 (65.1%)	0.91
	GG	11 (5.1%)	6 (4.8%)	0.88
	A	270 (62.2%)	158 (62.7%)	–
	G	164 (37.8%)	94 (37.3%)	0.89
rs1205171	CC	37 (17.4%)	20 (16.5%)	–
	CT	101 (47.6%)	57 (47.1%)	0.89
	TT	74 (35.0%)	44 (36.4%)	0.78
	C	175 (41.3%)	97 (40.1%)	–
	T	249 (58.7%)	145 (59.9%)	0.76
rs12151144	CC	128 (59.2%)	75 (59.5%)	–
	CT	76 (35.2%)	44 (34.9%)	0.96
	TT	12 (5.6%)	7 (5.6%)	0.99
	C	332 (76.9%)	194 (77.0%)	–
	T	100 (23.1%)	58 (23.0%)	0.97
rs7540065	AA	29 (15.3%)	15 (13.6%)	–
	AG	90 (47.4%)	52 (47.3%)	0.76
	GG	71 (37.3%)	43 (39.1%)	0.67
	A	148 (39.0%)	82 (37.3%)	–
	G	232 (61.0%)	138 (62.7%)	0.68
rs912767	AA	89 (40.4%)	54 (41.9%)	–
	AG	108 (49.1%)	62 (48.1%)	0.81
	GG	23 (10.5%)	13 (10.0%)	0.85
	A	286 (65.0%)	170 (65.9)	–
	G	154 (35.0%)	88 (34.1%)	0.81
rs7314	CC	44 (22.7%)	23 (21.1%)	–
	CT	92 (47.4%)	52 (47.7%)	0.80
	TT	58 (29.9%)	34 (31.2%)	0.73
	C	180 (46.4%)	98 (45.0%)	–
	T	208 (53.6%)	120 (55.0%)	0.73

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Conflict of interest None.

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