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Polymorphism and CDC25A Gene Expression in Pancreatic Cancer

Pankreas Kanserindeki CD25A Gen Ekspresyonu ve Polimorfizmi

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Abstract

Background and Aim: The aim of this study is to determine the relationship between CDC25A gene polymorphism and pancreatic cancer via determining CDC25A gene expression and polymorphisms of tumor tissues of pancreatic cancer cases. Additionally, it is aimed to prove the possible relationship between cancer development and the gene expression level with determining CDC25A gene expression levels in tumor tissue and normal tissue.

Materials and Methods: 118 patients (patients with pancreatic cancer who received surgery (n=28) and patients with pancreatic cancer who are in follow-up (n=90) and 83 healthy volunteers not having any known chronic disease and first degree relatives having cancer were included in this study as a control group.

Results: Ser88Phee polymorphisms in CDC25A gene of pancreatic cancer and control groups were compared according to C/C, C/T, T/T genotype frequencies and allele frequencies of C and T and no statistically significant difference was detected between two groups (p>0.05). RS3731485 polymorphisms in CDC25A gene of pancreatic cancer and control groups were compared with respect to C/C, C/G, G/G genotype frequencies and allele frequencies of C and G and there was no significant difference between them statistically (p>0.05). There were no differences in CDC25A gene expression between control group and pancreatic cancer group (p>0.05).

Conclusion: In the light of the data obtained, any significant relationship at the CDC25A gene polymorphism and expression in pancreatic cancer was not detected. All in all, pancreatic cancer is a disease with high mortality and the place of genetics in the etiology of cancer is indisputable. Therefore, we think the polymorphism and expression studies should be continued..

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Keywords: Pancreatic cancer, CDC25A, polymorphism, expression

Öz

Amaç: *Bu çalışmanın amacı pankreas kanser vakalarının tümör dokularının CDC25A gen ekspresyonu ve polimorfizmi belirlenmesi yoluyla CD25A gen polimorfizmi ve pankreas kanseri arasındaki ilişkinin belirlenmesi amaçlanmıştır.Ek olarak kanser gelişimi ve gen ekspresyon seviyesi ile normal doku ve tümör dokusundaki CD25A gen ekspresyonu arasındaki ilişkinin ihtimali amaçlanmıştır. .*

Materyal ve Metod: *118 hasta (pankreas kanseri nedeniyle ameliyat olan (n=28) hasta ve pankreas kanseri nedeniyle takip edilen (n=90) hasta, birinci derece akrabalarında kanser olan 83 sağlıklı gönüllü çalışmada kontrol grubu olarak çalışmaya dahil edildi.*

Bulgular: *Pankreas kanserinin ve kontrol gurubunun CD25A genindeki Ser88Phee polimorfizmi, C/C, C/T, T/T genotip sıklığı ve C ve T'nin alel sıklığı arasında yapılan karşılaştırmada iki grup arasında istatistiksel anlmalılık bulunmadı (p>0.05). Pankreas kanserinin ve kontrol gurubunun CD25A genindeki RS3731485 polimorfizmi, C/C, C/G, G/G, genotip sıklığı ve C ve G'nin alel sıklığı arasında yapılan karşılaştırmada iki grup arasında istatistiksel anlamlılık bulunmadı (p>0.05). pankreas kanser ve kontrol grupları arasında gen ekspresyonu açısından anlamlılık yoktu .*

Sonuç: *Elde edilen veriler ışığında pankreas kanserinde CD25A gen polimorfizmi ve ekspresyonu ile hiçbir anlamlı ilişki tespit edilmedi. Sonuçta pankreas kanseri yüksek mortaliteye sahip bir hastalıktır ve kanserin etiyolojisinde genetiğin yeri tartışılamaz. Bu yüzden polimorfizim ve ekspirasyon çalışmalarına devam edilmesini düşünüyoruz.* ***(Sakarya Tıp Dergisi 2016, 6(1):7-13)***

Anahtar Kelimeler: *Pankreas kanseri, CDC25A, Polimorfizim, Ekspresyon*

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INTRODUCTION

Pancreatic cancer is the most common cause of mortality associated with gastrointestinal cancer and is the fourth most common cause of cancer-related death in the United States[1]. In the same way, 5-year survival rate is unfortunately less than 5 % due to the late presentation of patients widely affected so it also makes therapeutic intervention difficult.[2] Surgical resection is the only method for potential treatment, however, this is only applied to only 10-20 % of patients with pancreatic cancer.[3] 5-year survival of the patients to whom pancreatoduodenectomy (Whipple procedure) is applied is healed and approaches to 20 %.[4] Significantly, when cancers smaller than 2 cm in diameter are confined to the pancreas and detected at an early stage, 5-year survival is higher and may approach to 46 %[4]. For this purpose, the detection of early-stage pancreatic cancer including preneoplastic lesions in patients at average and high risk (they are labeled as pancreatic intraepithelial neoplasia or PanIN) can significantly provide an opportunity to reduce pancreatic cancer mortality.

There is a period of approximately 10-20 years in the development of most cancers and this period is a sufficient period for preventive treatment. Overexpression of CDC25a has been reported in many human cancers. Even, the over-expression of this gene is associated with the extreme aggressiveness of the disease and poor prognosis[5].

CDC25 phosphatases are involved in cell differentiation, tumorigenesis, cell cycle checkpoints and apoptosis[6]. Because of the roles of CDC25 phosphatases about the fate of the cell, they should be tightly regulated during the cell division cycle. Also, CDC25 phosphatases should be inactivated in the checkpoint activation response in order to stop the progression of the cell cycle and to allow time to the cell for DNA repair or apoptosis. Wrongly editing any of these processes can result in genomic instability.

In a study made on head and neck cancer, over-expression of CDC25A and CDC25B has been worked with quantitative RT-PCR method. It was reported that CDC25 mRNA is over-expressed in 80% of cases and it was expresses 5 times more in 55% of them when compared to normal mucosa control[7]. CDC25A and CDC25B over-expression was observed in human gastric carcinoma[8].

In another study performed, gene structures of three isoforms and also splice variants, mRNA and protein expressions of CDC25 phosphatases were studied in human colorectal cancer and their relationship with patients' development and tumor pathological characteristics were evaluated. It has been shown that these phosphatases were regulated differently in colorectal carcinomas and could be included in the tumor development. The expression levels were found to be correlated with the lifetime and clinicopathological characteristics of the patient[9].

It has been reported that CDC25A was over-expressed in 47% of early stage breast cancer cases and this situation is associated with bad situation[10]. In another study investigating CDC25A and CDC25B expression levels immunohistochemically in breast cancer, similar results were obtained. In 69.6% of cases, high level of CDC25A has been reported[11].

CDC25A phosphatase is thought to have a place in the diagnosis and treatment of cancer due to over-expression observed in many cancer types and its critical role in cell cycle control. Although CDC25A was studied and found high in many cancer cases, there is only one study with pancreatic cancer. In that study, it was observed that the expression of CDC25B from CDC25 gene family was high but CDC25A and CDC25C had normal expression levels in contrast to other cancer cases. Data of 48 patients were evaluated and gene expression was only investigated in this study[12].

In this study, our aim is to determine the relationship between CDC25A gene polymorphisms with pancreatic cancer by putting out CDC25A gene expression and polymorphisms in the tumor tissues of pancreas cancer patients. For this purpose, we tried to make the literature data more comprehensive by determining CDC25A expressions in normal and cancerous tissues of 28 patients who received surgery and CDC25A polymorphisms in blood of 118 patients and 83 healthy individuals.

MATERIALS and METHODS

Study Populations

28 pancreatic cancer patients who received surgery, 90 pancreatic cancer patients without surgery and 83 healthy individuals were included into the study group. Tumor and neighboring healthy tissues from material taken in operation from 28 pancreatic cancer patients operated in Department of General Surgery according to treatment protocols were obtained and placed in a nitrogen tank. In addition, blood samples were taken from a total of 90 pancreatic cancer patients followed by Department of Medical Oncology and stored at -20 °C until DNA isolation procedure. For polymorphism study, blood samples were taken from 83 volunteers who they and their first-degree relatives didn't have a cancer history. The study was approved by the Institutional Review Board of Faculty of Medicine in XXX University (Ethic Committee Voucher no: 24.05.2010/5).

DNA and RNA Isolation

For DNA isolation from blood, peripheral blood samples (5 ml) were collected by venipuncture into sterile siliconized vacuum tubes with 2 mg/ml disodium EDTA. Immediately after collection, whole blood was stored at -20 °C until its use. Genomic DNA was extracted from whole blood using standard proteinase K digestion and after the salting-out, stored at -20 °C. For DNA isolation from both tumor and adjacent normal pancreas tissues, High Pure Template Preparation Kit (Roche, Mannheim, Germany) was used.

For RNA isolation from both tumor and adjacent normal pancreas tissues of 28 patients, High Pure RNA Tissue Kit (Roche, Mannheim, Germany) was used.

Expression Analysis

RNA samples obtained from tumor and adjacent normal pancreas tissues were converted to cDNA by using Precision qScript Reverse Transcription (PrimerDesign, Southampton, UK). Veriti™ Dx 96-Well Thermal Cycler (Applied Biosystem, Foster City, CA, USA) was used in thermal cycling processes in obtaining cDNA. PCR was performed using MJ Research PTC-200 PCR Machine (GMI, Minnesota, USA) for CDC25A expression. The sets of primers designed for CDC25A were forward 5'-GCTGCAGGGTCTGGGCAGTGAT-3' and reverse 5'-TCTGTTGACTCGGAGGAGCCCA-3' and for GAPDH were forward 5'-AGACCACAGTCCATGCCATCAC-3' and reverse 5'-GGTCCACCACCCTGTTGCTGT-3' as housekeeping gene.

Restriction Fragment Length Polymorphism (Rflp)

Before RFLP experiments, PCR optimization was realized for 2 pairs of primers designed for Ser88Phe and rs3731485. Nucleotide sequences of the PCR primer sets, sizes of the amplicons, and annealing temperatures are listed in Table 1. PCR optimization for each primer set was validated by temperature gradient. The thermo-cycling procedure consists of initial denaturation at 95 °C for 5 min, 34 cycles of denaturation at 94 °C for 30 s, annealing at temperatures given in Table 1 for 45 s for Ser88Phe and rs3731485 and extension at 72 °C for 30 s and final extension at 72 °C for 4 min. Amplification was achieved with in-house GeneAmp 9700 (Applied Biosystems, Foster City, CA, USA). Amplicons were resolved as a single band by 2% agarose gel electrophoresis, to ensure that a specific single product was amplified. To determine the SNPs on the CDC25A gene, PCR-RFLP technique has been used.

Table 1. Nucleotide sequences of the PCR primer sets designed for tracing the exons 3 and promoter region of CDC25A including the sizes of the amplicons.

Primers	Nucleotide composition (5'- 3')	Position	Expected size of PCR product (bp)	Annealing temperature (°C)
Ser88Phee Fw	TATTTGTTGC-CTGACTTA	Exon 3	253	52,7
Ser88Phee Rw	CTCCAGTC-CAGTGTATGA			
rs3731485 Fw	AGCCTAGCT-GCCATTCGG	Pro-moter	218	59,2
rs3731485 Rw	TTCGCT-GTTCTCC-CACCC			

The first polymorphic region, Ser88Phe, showed a C/T nucleotide transition in nucleotide 263 of the CDC25A gene. This nucleotide transition showed amino acid transition from Ser to Phe at amino acid position 88. This transition was identified by TfiI restriction enzyme and restricted on this region. The second polymorphic region, rs3731485, showed a C/G nucleotide transition in nucleotide -503 of the CDC25A gene

promoter region. This transition was identified by Bfal restriction enzyme and restricted on this region.

Statistical Analysis

SPSS 22.0 software (SPSS, Chicago, USA) and GraphPad Instat (GraphPad Software, San Diego, California, USA) were used for statistical analysis. Data was presented as mean and percentages. Fisher's chi-square test was used to compare genotype distributions and allele frequencies between groups. Relative quantification RT-PCR was performed in triplicate. Values were obtained as the threshold cycle (Ct) for CDC25A and normalized using the housekeeping gene and internal control, respectively. The ratio of the expression levels of CDC265A in tumor and control samples was used to determine expression change. The values below 0.5 and higher than 1.5 were considered as significantly increased and decreased. Mann-Whitney U test was used to compare expression levels. $P<0.05$ was considered as statistically significant.

RESULTS

28 pancreatic cancer patients who received surgery, 90 pancreatic cancer patients without surgery and 83 healthy individuals, who they and their first-degree relatives didn't have a cancer history, were included into the study group. Tumor and neighboring healthy tissues from material taken in operation from 28 pancreatic cancer patients operated in Department of General Surgery according to treatment protocols were obtained. Of 83 volunteers in control group, 43.3% was female[36] and 55.6% was male[47]. Of 118 pancreas cancer patients, 44.1% was female[52] and 55.9% was male[66]. Patient group's mean age was 64.2 (63.4 for female, 65 for male) and control group's mean age was 56.3 (57 for female, 55.6 for male).

When we evaluated the symptoms seen in the patients included in the study, we showed that the most frequently cause referred to the clinic was jaundice and weight loss. 59.3% (70 patients) of 118 patients included in the study had one or more comorbids (A total of 110 comorbids in 70 patients). The most common comorbid is diabetes mellitus (DM) with 59%. 68% (17 patients) and 32% (8 patients) of cardiovascular disease are hypertension (HT) and coronary artery disease (CAD), respectively. All of the respiratory disease was chronic obstructive pulmonary disease.

When our 118 patients were analyzed in terms of CA 19-9 and CEA as tumor markers, CA 19-9 and CEA levels were normal in 18.6% of patients (22 patients), CA 19-9 level was high and CEA level was normal in 54.2% (64 patients) and CA 19-9 and CEA levels were high in 27.1% (32 patients).

USG, abdominal CT, ERCP and MRCP were used for the patients as imaging methods. Abdominal CT and ultrasound were used most frequently. When all of 118 patients were evaluated according to their pathology reports, all of them were classified as adenocarcinoma in terms of pathological types.

When pancreatic cancer and control groups were classified for Ser88Phe polymorphisms of CDC25A gene in terms of C/C, C/T, T/T genotype frequencies, 97.5% (115 patients) had C/C, 0.8% (1 patient) had C/T and 1.7% (2 patients) had T/T genotype of the cancer group while 97.6% (80 patients) had C/C, 2.4% (2 patients) had C/T and no patient had T/T genotype of the control group. When pancreatic cancer and control groups were classified for Ser88Phe polymorphisms of CDC25A gene in terms of C and T allele frequencies, it was shown that 97.9% (231 patients) had C allele and 2.1% (5 patient) had T allele of the cancer group while 98.8% (162 patients) had C allele and 1.2% (2 patient) had T allele of the control group. When pancreatic cancer and control groups were compared or Ser88Phe polymorphisms of CDC25A gene in terms of C/C, C/T, T/T genotype frequencies and C and T allele frequencies, no statistically significant difference was detected ($p>0.05$, Table 2).

Table 2. Genotype distributions and allele frequencies for CDC25A gene Ser88Phe polymorphism in the patient and control groups.

Genotype	Control (n=82) n (%)	Patient (n=118) n (%)	p value	OR (95% CI)
Ser/Ser (C/C)	80 (97.6)	115 (97.5)		
Ser/Phe (C/T)	2 (2.4)	1 (0.8)	0.571	0.348 (0.031-3.904)
Phe/Phe (T/T)	0 (0.0)	2 (1.7)	0.515	3.485 (0.165-73.615)
Allele	Control n (%)	Patient n (%)	p value	OR (95% CI)
Ser (C)	162 (98.8)	231 (97.9)	0.705	1.753 (0.336-9.152)
Phe (T)	2 (1.2)	5 (2.1)		

When pancreatic cancer and control groups were classified for rs3731485 polymorphisms of CDC25A gene in terms of C/C, C/G, G/G genotype frequencies, 94.9% (112 patients) had C/C, 2.5% (3 patient) had C/G and 2.5% (3 patients) had G/G genotype of the cancer group while 92.2% (71 patients) had C/C, 5.2% (4 patients) had C/G and 2.6% (2 patients) had G/G genotype of the control group. When pancreatic cancer and control groups were classified for rs3731485 polymorphisms of CDC25A gene in terms of C and G allele frequencies, it was shown that 96.2% (227 patients) had C allele and 3.8% (9 patient) had G allele of the cancer group while 94.8% (146 patients) had C allele and 5.2% (8 patient) had G allele of the control group. When pancreatic cancer and control groups were compared or rs3731485 polymorphisms of CDC25A gene in terms of C/C, C/T, T/T genotype frequencies and C and T allele frequencies, no statistically significant difference was found (p>0.05, Table 3)

Table 3. Genotype distributions and allele frequencies for CDC25A gene rs3731485 polymorphism in the patient and control groups.

Geno-type	Control (n=77) n (%)	Patient (n=118) n(%)	p value	OR (95% CI)
C/C	71 (92.2)	112 (94.9)		
C/G	4 (5.2)	3 (2.5)		
G/G	2 (2.6)	3 (2.5)	0.437	0.475 (0.103-2.118)
Allele	Control n (%)	Patientn (%)	1.000	0.951 (0.155-5.835)
C	146 (94.8)	(n=118) n(%)	p value	OR (95% CI)
G	8 (5.2)	227 (96.2)	0.614	0.724 (0.273-1.918)
Fisher's chi-square test, OR: odds ratio				

CDC25A gene expression was studied in tumor and neighboring healthy tissues from material taken in operation from 28 pancreatic cancer patients operated in our study. Reference range was between 0.5 and 1.5. If the expression value was below 0.5, the expression was decreased. If the expression value was higher than 1.5, the expression was increased. If the expression value was between 0.5 and 1.5, the expression was normal. As a result of our result, the expression level was incresed in 7.14% (3 patients), decreased in 3,57% (1 patient) and normal in 89.28% (25 patients) of 28 patients (Figure 1). Statistical analysis performed on expression levels obtained showed that there was no statistically significant difference between pancreatic cancer and control groups in terms of CDC25A gene expression (p>0.05).

DISCUSSION

Many studies demonstrated different genetic and epigenetic alterations, including K-ras proto-oncogene and p53, Smad4/DPC4 and p16/CDKN2A tumor suppressor gene mutations, in PDAC[13]. Also, over-expression of growth factors and growth factor receptors is observed in most of these tumors and PDACs causes many important changes in regulatory pathways of apoptosis, invasion and metastasis[14-16]. PDAC is characterized by uncontrolled cell cycle progression, cell cycle arrest and resistance to apoptosis, and these are associated with both mutations in K-ras and p53 protooncogenes and Smad4/DPC4 and p16/CDKN2A tumor suppressor gene mutations[16]. CDC25A overexpression has been seen in many human cancers and this shows that it may take role in the development of malignant transformation and pathogenesis of these phosphatases. Therefore, we tried to evaluate the role of CDC25A gene in cell cycle progression by analyzing this gene expression and polymorphism in PDAC in this study.

Deregulation of cell cycle control mechanism is thought to play a key role in the malignant transformation of cells[17]. The changes in genes regulating the cell cycle are often encountered in human cancers[18] and the cell proliferation reflecting cell cycle progression contributes to the aggressive growth pattern of cancer cells. Two critical control points have been identified and are included in the G1-S phase and G2M phase change. The major components in the cell cycle system are cyclins and their corresponding cyclin dependent kinases (CDK). CDK/cyclin complexes are activated and deactivated sequentially to regulate the different phases of the cell cycle. The progress of the cell cycle deregulation in PDAC is associated a number of mutations in different genes; tumor suppressor p53 gene preventing anti-apoptotic responses and standby G1-S phase, K-ras providing continuation of cell proliferation and cell immortality[13] and CDKN2A encoding two tumor suppressors (INK4a and ARF) and leading uncontrolled cell cycle progression by disrupting retinoblastoma (RB) and p53 pathways can be considered among these genes[19].

CDC25A phosphatase is a new family of CDK phosphatases and their role is to activate CDK/cyclin complexes by dephosphorylating CDKs at different cell cycle checkpoints[20,21]. CDC25A is expressed in late G1 phase and controls G1/S transition by activating CDK2/cyclin E complex[22].

The CDC25B and C are very important for G2 phase and G2/M transition[23,24]. Expression of CDC25A phosphatase in PDAC was evaluated in 48 patients in only one study in the literature and was found to be not increased in contrast to other malignancy studies[12]. In our study, we have evaluated more thoroughly CDC25A gene expression in the 28 patients and CDC25A gene polymorphisms in 118 patients and 83 healthy individuals. CDC25A expression and polymorphism assessment remained within normal limits in accordance with previous study. In contrast, the fact that CDC25A expression didn't show a significant difference between the normal and cancer tissues was not compatible with with the data found in previous studies on other tumor types.

Any effect of CDC25A which is a member of CDC25 gene family serving as a control step in cell division has not been found in pancreatic cancer. However, CDC25 gene family expression results in some studies performed on pancreatic cancer have shown that CDC25B has been responsible for pancreatic cancer[12].

CONCLUSION

These results show that CDC25A from CDC25 gene family is not a gene taking active role in pancreatic cancer. However, the fact that CDC25A expression and polymorphism results are in normal range in pancreatic cancer doesn't mean that this gene has not any effect in pancreatic cancer. For better understanding of this case, examining the genetic pathway taking role in the regulation of CDC25A gene would provide real role of CDC25A gene in pancreatic cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee for Clinical Research (Ethic Committee Voucher no: 24.05.2010/5).

Conflict of Interest:

No conflict of interest was declared by the authors.

Financial Disclosure:

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