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BRIEF ARTICLE

Role of *cyclooxygenase-2* gene polymorphisms in pancreatic carcinogenesis

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Abstract

AIM: To evaluate the clinical significance of *-765G/C* and *-1195G/A cyclooxygenase-2 (COX-2)* gene polymorphisms in patients with pancreatic cancer (PC).

METHODS: The study included 201 patients: 85 with PC and 116 healthy controls. *-765G/C* and *-1195G/A COX-2* gene polymorphisms were studied in DNA isolated from blood samples. The associations of the analyzed genotypes and clinical data at diagnosis were evaluated.

RESULTS: We found an increased frequency of the homozygous *-1195AA COX-2* genotype in patients with PC (53.7%) compared with the control group (21%) ($P < 0.01$). In contrast, the distribution of genotype and allele frequencies of the *-765G/C COX-2* polymorphism in the PC patients were not different from those in control groups. A correlation between presence of homozygous *-1195AA COX-2* genotype and tumor size > 3 cm was observed ($P < 0.05$). Analyzed polymorphisms were unrelated to the patients' sex and age, nor to the presence of regional or distant metastases.

CONCLUSION: These preliminary results indicate that the *-1195G/A COX-2* polymorphism may play an important role in PC prognosis and carcinogenesis.

Key words: *Cyclooxygenase-2*; Polymorphisms; Pancreatic cancer; Carcinogenesis

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INTRODUCTION

Cyclooxygenase-2 (COX-2), also known as prostaglandin endoperoxide synthase, is a key enzyme in the arachidonic acid pathway, initiating the synthesis of biologically important prostanoids and eicosanoids. *COX-2* is involved in many biologic processes, such as cell proliferation, invasion, angiogenesis and inhibition of apoptosis, which are all relevant to cancer development and progression[1].

COX-2 is expressed under certain extracellular or intracellular stimuli, such as mitogens, growth factors, hormones, infectious agents and proinflammatory cytokines[1,2]. Numerous studies have demonstrated increased expression of *COX-2* in various cancers, including pancreatic tumors[3-6]. In several studies, the overexpression of *COX-2* in pancreatic cancer (PC) cells has been shown to be an independent prognostic factor and to increase the clinical aggressiveness of this disease[3,4,7].

The *COX-2* gene was demonstrated to be genetically polymorphic, which may affect the expression or activity of this enzyme and consequently contribute to variation in individual susceptibility to cancer through aberrant arachidonic acid metabolism. Genetic variants represented by single nucleotide polymorphisms (SNPs) of the *COX-2* gene, among them *-765G/C* and *-1195G/A* in the promoter region, have been identified. The functional effects of these SNPs have been recently confirmed[8-10]. The *-765G* allele is associated with heightened *COX-2* transcription by creating a transcriptional factor c-MYB-binding site and with significantly higher promoter activity compared with *-765C* allele[8,9]. In the study of Zhang *et al*[10], the *-1195A*-containing haplotypes also had significantly increased *COX-2* messenger RNA levels in esophageal tissues compared with the *-1195G*-containing counterparts.

COX-2 has been the object of prevention/intervention strategies in many clinical trials, including being a potential therapeutic target for chemoprevention and therapy of PC[1,2,11]. Selective inhibition of *COX-2* results in variable responses in individual patients. Information regarding the functional significance of *COX-2* polymorphisms with risk-modulating ability would have significant implications, not only for risk identification, but also for pharmacological management of the disease.

The purpose of this study was to evaluate the clinical significance of *-765G/C* and *-1195G/A COX-2* gene polymorphisms in patients with PC.

MATERIALS AND METHODS

The study included 201 Caucasian patients: 85 with PC (41 men and 44 women, aged 44-84 years) and 116 gender- and age-matched healthy volunteers. Analyzed patients were hospitalized in the Department of Digestive Tract Diseases, Medical University of Lodz Hospital or in the Department of Digestive Tract Surgery of Silesian Medical University in Katowice between 2004 and 2009. Only patients with a confirmed pathological diagnosis of ductal pancreatic adenocarcinoma were included in the study. The pathological diagnosis was confirmed after surgical treatment or after pancreatic tissue biopsy in patients who qualified for palliative chemotherapy. Twenty-nine patients (34.1%) with PC underwent Whipple resection or distal pancreatectomy, 33 patients (38.8%) underwent palliative surgery and 23 patients (27.1%) underwent palliative chemotherapy and/or endoscopic treatment. Tumor grade was classified into G1 (well differentiated), G2 (moderately differentiated) and G3 (poorly differentiated). The study protocol was approved by the ethical committee of Lodz Medical University.

Peripheral venous blood samples were obtained from all analyzed patients at the time of hospital admission. *-765G/C* and *-1195G/A COX-2* gene polymorphisms were studied in DNA isolated from blood samples using the QIAmp DNA Mini Kit (Qiagen). Polymerase chain reaction (PCR) products for the *COX-2* variants were analyzed by the restriction fragment length polymorphism method. The primers used to amplify the *COX-2* promoter region were 5'-TAT TAT GAG GAG AAT TTA CCT TTC GC-3' and 5'-GCT AAG TTG CTT CAA CAG AAG AAT-3' for the *-765G/C* variant; and 5'-CCC TGA GCA CTA CCC ATG AT-3' and 5'-GCC CTT CAT AGG AGA TAC TGG-3' for the *-1195G/A* polymorphism. PCR amplification was per-formed in a final volume of 25 μL containing 30-100 ng of DNA, 10 mmol/L Tris-HCl (pH 8.3), 4 μL of 25 mmol/L $MgCl_2$, 50 mmol/L KCl, 0.5 μL dNTP (10 mmol/L), each primer at 1.0 μmol/L and 1.0 unit of Taq polymerase (BIOKOM, Takara, Japan) in a GeneAmp PCR system 9700 Thermocycler (Applied Biosystems).

Ten microliters of the PCR product were digested with 2 units of restriction enzymes HhaI or Pvu Ⅱ (Bio-Laps, New England) using the manufacturer's recommended protocol. PCR products were visualized on 8% polyacrylamide gels with 10% ethidium bromide. *COX-2* genotypes that could be detected were respectively: *-765CC* (100 bp fragment), *-765GC* (100 and 74 and 26 bp fragments), *-765GG* (74 and 26 bp fragments), *-1195AA* (273 bp fragment), *-1195GA* (273 and 220 and 53 bp fragments) and *-1195GG* (220 and 53 bp fragments).

The serum concentrations of CA19-9 were measured by an enzyme-linked immunoassay (DRG International, United States), according to the manufacturer's recommendations. The associations of the analyzed genotypes and patient characteristics at PC diagnosis were evaluated. The following demographic and clinical data were analyzed: age, gender, tumor size, lymph node involvement, histological grade, CA19-9 levels, weight loss and history of smoking. The cut-off point of CA19-9 was set at 37 U/mL.

Statistics analysis

The results were analyzed using StatSoft Statistica for Windows, release 6.0 (StatSoft, Inc., Tulsa, United States). To determine differences between groups, Mann-Whitney *t* tests were used. Clinical significance of analyzed polymorphisms was determined using logistic regression analysis and presented in tables as odds ratios (OR) with their 95% confidence intervals. The deviations from Hardy-Weinberg equilibrium were analyzed using the χ^2 test. Differences with a *P* value less than 0.05 were considered significant.

RESULTS

All patients involved in the study were Caucasians. Mean ages were not significantly different for patients with PC

Table 1 Distribution of *-1195 G/A* and *-765 G/C COX-2* genotype in the analyzed group of patients *n* (%)

Genotype	PC patients (*n* = 85)	Control group (*n* = 116)	OR (95% CI)
-1195 G/A			
GG	13 (15.7)	44 (37.9)	Reference
GA	26 (30.6)	48 (41.4)	1.83 (0.84-4.00)
AA	46 (53.7)	24 (21.0)	6.48 (2.93-14.31)
- 765 G/C			
GG	47 (55.4)	44 (37.9)	Reference
GC	27 (31.7)	40 (34.5)	0.63 (0.33-1.19)
CC	11 (12.9)	32 (27.6)	0.32 (0.14-1.71)

PC: Pancreatic cancer; OR: Odds ratios.

Table 2 Relationship between *-1195 G/C COX-2* polymorphism and clinical data of patients with pancreatic cancer *n* (%)

	Group	G^+ allele (GA and GG) (*n* = 39)	*P* value	G^- allele (AA) (*n* = 46)	*P* value
Age	< 65	20 (51.3)	NS	19 (41.3)	NS
	⩾ 65	19 (48.7)		27 (58.7)	
Gender	Male	18 (46.2)	NS	23 (50.0)	NS
	Female	21 (53.8)		23 (50.0)	
Tumor size	⩽ 3 cm	21 (53.8)	NS	13 (28.3)	*P* < 0.05
	> 3 cm	18 (46.2)		33 (71.7)	
Tumor	G1 + G2	21 (53.8)	NS	27 (58.7)	NS
Differentiation	G3	17 (43.8)		18 (39.2)	
Lymph node	Absent	23 (58.9)	NS	23 (50.0)	NS
Metastases	Present	16 (41.1)		23 (50.5)	
Weight loss	< 10 %	19 (48.7)	NS	25 (54.4)	NS
	⩾ 10%	20 (51.3)		21 (45.6)	
Smoking	Yes	21 (53.8)	NS	19 (41.3)	NS
	No	18 (46.2)		27 (58.7)	
CA19-9	< 37 U/mL	10 (25.6)	NS	13 (28.3)	NS
	⩾ 37 U/mL	29 (74.4)		33 (71.7)	

NS: Not significant.

Table 3 Relationship between *-765 G/C COX-2* polymorphism and clinical data of patients with pancreatic cancer *n* (%)

	Group	G^+ allele (GC and GG) (*n* = 47)	*P* value	G^- allele (CC) (*n* = 38)	*P* value
Age	< 65	23 (48.9)	NS	16 (42.1)	NS
	⩾ 65	24 (51.1)		22 (57.9)	
Gender	Male	22 (46.8)	NS	19 (50.0)	NS
	Female	25 (53.2)		19 (50.0)	
Tumor size	⩽ 3 cm	17 (40.4)	NS	15 (39.5)	NS
	> 3 cm	28 (59.6)		23 (60.5)	
Tumor	G1 + G2	27 (57.4)	NS	21 (55.3)	NS
Differentiation	G3	20 (40.4)		16 (42.1)	
Lymph node	Absent	28 (59.8)	NS	18 (47.4)	NS
Metastases	Present	19 (40.4)		20 (52.6)	
Weight loss	< 10 %	30 (63.8)	NS	21 (55.3)	NS
	⩾ 10%	17 (36.2)		17 (44.7)	
Smoking	Yes	23 (48.9)	NS	17 (44.7)	NS
	No	24 (51.1)		21 (55.3)	
CA19-9	< 37 U/mL	12 (25.5)	NS	12 (31.6)	NS
	⩾ 37 U/mL	35 (74.5)		26 (68.4)	

NS: Not significant.

(mean 66.8 ± 4.1 years) and controls (63.1 ± 4.7 years, $P > 0.05$). In patients with pancreatic adenocarcinoma, the tumor size ranged from 2 cm to 7 cm (mean 3.7 ± 2.3). As for histological differentiation, 19, 29 and 35 patients were classified into G1, G2 and G3 respectively, whereas 2 patients had missing data. Lymph node metastases were observed in 39 patients with PC (45.9%) and liver metastases in 16 of them (18.8%). Serum levels of CA19-9 were higher in patients with PC compared to control group ($P < 0.001$; respectively 101.2 ± 21.4 U/mL *vs* 17.6 ± 3.2 U/mL; data shown in our previously published work[22]).

The genotype distributions of analyzed *-765G/C* and *-1195G/A COX-2* gene polymorphisms are summarized in Table 1. We found an increased frequency of the homozygous *-1195AA COX-2* genotype in patients with PC compared with control group [OR 6.48 (2.93-14.31), $P < 0.01$]. In contrast, the distribution of genotype and allele frequencies of the *-765G/C COX-2* polymorphism in the PC patients did not differ from those in control groups (Table 1). Each of the *COX-2* polymorphisms in the controls was consistent with Hardy-Weinberg equilibrium.

The potential relationship between *COX-2* genotype distribution and clinical data of the PC patients was investigated. *COX-2 -1195AA* genotype showed a significant association with tumor size > 3 cm in patients with PC ($P < 0.05$, Table 2). This analyzed polymorphism was unrelated to the patients' sex and age, weight loss, history of smoking, CA19-9 levels, nor with the presence of regional or distant metastases. In contrast, the *-765G/C COX-2* polymorphism was not associated with any clinical data (Table 3).

DISCUSSION

The overexpression of COX-2 has been shown to induce angiogenesis by increased synthesis of vascular endothelial growth factor and to inhibit apoptosis by activation of proto-oncogene Bcl-2[2]. It is known that the expression of COX-2 is increased in the majority of PC cells and may represent a target for adjuvant therapy of PC. However, little is known about the role of *COX-2* gene polymorphisms in pancreatic carcinogenesis. We investigated the clinical significance of the *-765G/C* and *-1195G/A COX-2* gene polymorphisms, as well as their potential association with the risk of developing PC.

In our study, the presence of the *-1195AA* genotype was found more frequently in patients with PC compared to the control group. Similarly, Zhao *et al*[8] observed that subjects carrying the *COX-2 -1195A* allele had significantly increased risk for developing PC compared with subjects carrying the *-1195G* allele. In previous studies, the association of the *-1195A* allele with an increased risk of lung, oral and esophageal cancers was also demonstrated[12-14]. In the study of Bi *et al*[13], *-1195AA* genotype was significantly correlated with worse overall survival (15.7 mo *vs* 20.2 mo, $P = 0.006$) and with shorter

progression-free survival (9.5 mo *vs* 11.9 mo, $P = 0.0034$) in patients with unresectable locally advanced non-small cell lung cancer.

However, others authors observed opposite results. In the study of Kristinsson *et al*[15], the *-1195GG* genotype resulted in a higher risk of developing esophageal adenocarcinom. On the other hand, Pereira *et al*[16] observed that men carrying the *-1195G* allele appeared to have a nine-fold increased risk for colorectal cancer. Racial and ethnical differences in the studies' populations may explain these contradictory results, because the distribution of *COX-2* polymorphisms may differ considerably between populations.

The published data about clinical significance of the second analyzed polymorphism of *COX-2* gene, *-765G/C*, are also controversial. In the study of Hoff *et al*[17], the *-765GG* genotype was present more often in patients with colorectal cancer compared to control group. Similarly, Coskunpinar *et al*[14] observed increased risk of lung carcinoma in Turkish patients carrying the *-765G* allele. In contrast, the *-765C* allele was associated with an increased risk for developing PC and urinary bladder cancer[8,18]. This is not in line with our findings, since we could not demonstrate a significant difference in *-765G/C* genotype distribution in patients with PC. Similarly, Dong *et al*[19] in a meta-analysis of 47 case-control studies did not find a convincing association between *-765G/C COX-2* gene polymorphism and the risk of cancer in diverse populations.

Another important aspect of our analysis was to assess the potential association of *-765G/C* and *-1195G/A COX-2* gene polymorphisms with clinical data of patients with PC. In the current study, the homozygous *-1195AA* was found to be present more frequently in patients with larger tumor size. To the best of our knowledge there are no available data about relationships between *-1195G/A COX-2* polymorphism and clinical characteristics of patients with PC. Earlier, Tan *et al*[20] demonstrated that the *COX-2 -1195A* allele was associated with the presence of distant metastases in patients with colorectal cancer. They suggested that COX-2 may play a role not only in colorectal tumorigenesis but also in cancer progression by stimulating cell proliferation and spread.

According to our data, the second analyzed *COX-2* polymorphism, *-765G/C*, was not associated with clinical parameters. Similarly, in other studies the *-765G/C* variant was not correlated with clinical stage of patients with cervical and colorectal cancers[17,21].

Overexpression of *COX-2* may be an important cellular mechanism in smoking-related PC development. Numerous studies have shown that smoking induces *COX-2* expression, but the exact signal pathways remain to be elucidated. Zhao *et al*[8] suggested that *COX-2* genetic polymorphisms may determine interindividual variation in the inducibility of *COX-2* expression. They observed that smoking remarkably increased *COX-2* promoter activity, especially in patients with PC carrying the *-765C* allele. In contrast, in our study, there was no association between analyzed polymorphisms and smoking. Similarly, Pandey *et al*[21] did not find a correlation between smoking and *COX-2* polymorphisms in patients with cervical cancer. This lack of association could be due to a relatively small number of subjects and certainly needs further validation.

In summary, we found a significant difference in the *-1195G/A COX-2* gene polymorphism distribution between patients with PC and the control group. The presence of *-1195AA* genotype was associated with an increased PC risk; however, further studies are needed to investigate its possible association with PC prognosis. Our results are consistent with the biological function of the polymorphisms and support the hypothesis that aberrant arachidonic acid metabolism may play an important role in pancreatic carcinogenesis.

COMMENTS

Background

Despite improved diagnostic and therapeutic capabilities, pancreatic cancer (PC) still has a very poor prognosis. Numerous studies suggest a role for *cyclooxygenase-2 (COX-2)* in pancreatic carcinogenesis. *COX-2* is involved in many biologic processes, such as cell proliferation, invasion, angiogenesis and inhibition of apoptosis, which are all relevant to cancer development and progression.

Research frontiers

The *COX-2* gene was demonstrated to be genetically polymorphic, which may affect the expression or activity of this enzyme and consequently contribute to variation in individual susceptibility and aggressiveness of PC.

Innovations and breakthroughs

This study analyzed the clinical significance of *-765G/C* and *-1195G/A COX-2* gene polymorphisms in patients with PC. In the study, the presence of the *-1195AA* genotype was associated with an increased risk of PC; however, further studies are needed to investigate its possible association with PC prognosis.

Applications

The results are consistent with the biological function of the polymorphisms and support the hypothesis that aberrant arachidonic acid metabolism may play an important role in pancreatic carcinogenesis.

Terminology

COX-2 is a key enzyme in the arachidonic acid pathway, initiating the synthesis of biologically important prostaglandin H2 (the precursor of other prostaglandins), prostacyclin and tromboxanes.

Peer review

In this manuscript, the authors demonstrate that *COX-2* gene polymorphisms might be associated with carcinogenesis of PC. A series of experiments are well-planned and well-performed and this manuscript is well written.

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