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ORIGINAL ARTICLE

Case Control Study

Genetic polymorphisms of *interleukin 1β* gene and sporadic pancreatic neuroendocrine tumors susceptibility

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Abstract

AIM: To evaluate the association between the interleukin 1β (IL-1β) polymorphisms and the pancreatic neuroendocrine tumor (pNET) development.

METHODS: A case-control study was conducted analyzing IL-1β polymorphisms using germline DNA collected in a population-based case-control study of pancreatic cancer (51 pNET cases, 85 pancreatic ductal adenocarcinoma cases, 19 intraductal papillary mucinous neoplasm and 98 healthy controls).

RESULTS: The distribution of genotypes for the -511

C/T polymorphism in the pNET patient groups showed significant difference compared to the control group. It is known that the carriers of the IL-1β -511T allele have increased concentrations of IL-1β. The -511 CT and TT high-expression genotypes were over-represented in pNET patients.

CONCLUSION: The findings of this study suggested a possible role of IL-1β -511 C/T genotypes in the pathogenesis of pNETs since the presence of the IL-1β -511 CT and TT genotypes and the T allele was associated with an increased risk of pNET only.

Key words: Interleukin 1β; Neuroendocrine tumors; Pancreas

Core tip: Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous group of rare neoplasms derived from pancreatic endocrine cells and have significantly different tumor biology and present better prognosis compared with tumors of the exocrine pancreas, like pancreatic adenocarcinomas. It is widely accepted that chronic inflammation contributes to pathogenesis of many pancreatic diseases, including pancreatic carcinogenesis. Interleukin 1β (IL-1β) is a highly active pro-inflammatory cytokine with multiple biological effects, such as directing cancer cells to either neuroendocrine differentiation or to development of adenocarcinoma. The purpose of the study was to evaluate the association between the IL-1β polymorphisms and the pNET development.

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INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous group of rare neoplasms derived from pancreatic endocrine cells[1-5]. The annual incidence of pNETs is estimated to be approximately 3.65 per 100000 individuals in the United States and occur sporadically or may be associated with genetic syndromes such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau syndrome (VHL), von Recklinghausen disease (neurofibromatosis NF-1), and tuberous sclerosis complex (TSC)[6-8].

PNETs are mainly considered functionally inactive tumors, but when related with hormone or peptide overproduction, such as insulin, gastrin, glucagon, vasoactive intestinal polypeptide (VIP) and somatostatin they are responsible for many characteristic clinical syndromes, with insulinoma being the most common PNETs are usually asymptomatic[9,10], have significantly different tumor biology, and present better prognosis compared with tumors of the exocrine pancreas, like pancreatic adenocarcinomas (PDACs)[11].

The molecular basis of pNETs pathogenesis is poorly characterized but several recent reports have been conducted in order to clarify their etiology[12].

It is widely accepted that chronic inflammation contributes to pathogenesis of many pancreatic diseases, including pancreatic carcinogenesis[13,14]. However, the exact mechanism by which chronic inflammation promotes carcinogenesis is still unknown. During carcinogenesis the host-mediated anti-tumor activity is suppressed, whereas pro-inflammatory events support tumor growth, angiogenesis, invasion and metastasis[15]. The inflammatory response is mediated by cytokines, which are glycoproteins or soluble proteins and their role in cancer immunity and carcinogenesis has been well established[16-18].

Neuroendocrine tumors express various cytokines and growth-factors. Several pro-inflammatory cytokines have been found in pNETs tissue suggesting their involvement in pNET development[19-21]. Additionally, numerous studies suggested that gastroenteropancreatic-NETs occur more frequently in the environment of chronic inflammation[22-24]. Thus, cytokines such as interleukin 1 (IL-1) poses an important role in neuroendocrine tumors since direct cancer cells to either neuroendocrine differentiation or to development of adenocarcinoma, while exogenously added IL-1 results in a decrease of chromogranin A (CgA) and simultaneous increase in carcinoembryonic antigen (CEA) secretion[25].

IL-1β is a highly active pro-inflammatory cytokine with multiple biological effects[26]. IL-1β protein levels are related to the intensity of the inflammatory response, and regarding to pancreas, IL-1β is implicated in cancer progression, especially tumor invasiveness, metastasis and angiogenesis[27,28].

The *IL-1β* gene is located in the IL1 cluster on chromosome 2q and several single nucleotide polymorphisms (SNPs) of this gene influence the regulation of its expression and function have been studied[29-32]. There are two SNPs in the proximal promoter region of the *IL-1β* gene, -511 C/T and +3954 T/C, which both have been correlated with gastrointestinal cancers, such as gastric, hepatocellular cancer (HCC) and pancreatic cancer[33-36]. Recently, Cigrovski Berković *et al*[37] reported that the *IL-1β* -511 SNP contributes to the pNET susceptibility.

We conducted a case-control study to analyze *IL-1β* polymorphisms as risk factors for pNETs using germline DNA collected in a population-based case-control study of pancreatic cancer [51 pNET cases, 85 PDAC cases, 19 intraductal papillary mucinous neoplasm (IPMN) and 98 healthy controls] conducted in the Athens, Greece and Izmir, Turkey areas.

MATERIALS AND METHODS

Patients

The case-control study included 51 pNET cases (22

Table 1 Characteristics of the patients and controls *n* (%)

Characteristic	PDAC	pNET	IPMN	Controls
Total number	85	51	19	98
Mean age (yr)	59.12	56.31	57.91	58.9
Gender				
Male	51 (60)	20 (39.2)	11 (57.9)	74 (75.5)
Female	34 (40)	31 (60.8)	8 (42.1)	24 (24.5)
Tumor stage				
Ⅰ	13 (15.3)			
Ⅱ	36 (42.4)			
Ⅲ	33 (38.8)			
Ⅳ	3 (3.5)			
G stage				
G1		35 (68.6)		
G2		14 (27.5)		
G3		2 (3.9)		
Tumor location				
Head	64 (75.3)	19 (37.3)	7 (36.8)	
Body and tail	21 (24.7)	32 (62.7)	12 (63.2)	
Differentiation status				
Well	10 (11.8)			
Moderate	39 (45.9)			
Poor	36 (42.3)			

pNET: Pancreatic neuroendocrine tumor; PDAC: Pancreatic adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasm.

nonfunctional and 29 functional), 85 PDAC cases, 19 IPMN and 98 healthy controls (Table 1). None of the cases had a history of chronic pancreatitis. For subsequent analysis, we excluded cases and controls with known genetic syndromes (*e.g.*, MEN1, MEN2, VHL or TSC). Controls were healthy blood donors with no evidence of inflammation. The diagnosis in all cases was established by standard procedures and confirmed histopathologically either from operatively resected tumors or biopsy tissues, in cases of unresectable tumors. Before commencement of the study, the Ethical committee at the participating centers approved the recruitment protocols. All participants were informed regarding the study, and their written consent was provided.

Genotyping

Genomic DNAs were isolated from peripheral ethylenediaminetetraacetic acid-treated blood of patients and healthy controls using the NucleoSpin Blood Kit (Macherey-Nagel, Germany). The *IL-1β* -511 C/T (rs16944) polymorphism was detected by PCR-RFLP using the set of primers: 5′-TGGCATTGATCTGGTTCATC-3′ and 5′-GTTTAGGAATCTTCCCACTT-3′. The 35 cycles of PCR were carried out at 94 ℃ for 5 min, 94 ℃ for 1 min, 58 ℃ for 40 s and 72 ℃ for 1 min and the final cycle of 72 ℃ for 5 min. Amplified PCR products were digested with *Ava*I for 2 h at 37 ℃. The fragments of 189- and 116-bp revealed homozygosity for the C allele, and 305-bp indicated homozygosity for the T allele. The +3954 C/T (rs 1143634) polymorphism was detected with the 5′-TCAGGTGTCCTCGAAGAAATCAAA-3′ and 5′-GGTTTTTTGCTGTGAGTCCC-3′ set of primers and the cycling parameters for that was 94 ℃ for 5 min, 94 ℃ for 45 s, 56 ℃ for 45 s and 72 ℃ for 45 s and the final cycle of 72 ℃ for 5 min. After 35 cycles the PCR product were digested for 2 h at 65 ℃ with *Taq*I. The fragments of 97- and 85-bp revealed homozygosity for the C allele and on the other hand 182-bp fragments showed homozygosity for the T allele.

Statistical analysis

Genotype frequencies were compared with the χ^2 with Yate's correction using S-Plus (v. 6.2, Insightful, Seattle, WA). Odds ratios (ORs) and 95%CIs were obtained with GraphPad (v. 3.00, GraphPad Software, San Diego, CA). The *P* values are all two-sided, and *P* values of < 0.05 were considered to be significant. Hardy-Weinberg equilibrium was verified by calculating the expected frequencies and numbers and was tested separately in patients and in controls using the goodness-of-fit χ^2 test. Haplotype analysis was performed using the http://bioinfo.iconcologia.net/SNPstats software.

RESULTS

The clinicopathological characteristics of the studied population are summarized in Table 1. The genotype frequencies of the *IL-1β* -511 C/T and +3954 C/T polymorphisms between PDAC, pNET, IPMN patients and controls are given in Table 2. All genotype distributions were in Hardy-Weinberg equilibrium. The distribution of genotypes for the -511 C/T polymorphism in the pNET patient groups only showed significant difference compared to the control group. It is known that the carriers of the *IL-1β* -511T allele have increased concentrations of IL-1β[38]. The -511 CT and TT high-expression genotypes were over-represented in pNET patients (Table 2). However, the presence of the +3954T

Table 2 Genotype and allele frequencies of the interleukin 1β -511 C/T and +3954 C/T polymorphisms in pancreatic adenocarcinoma, pancreatic neuroendocrine tumor and intraductal papillary mucinous neoplasm patients and controls

	Controls (n = 98)	PDAC (n = 85)	P; OR (95%CI)	pNET (n = 51)	P; OR (95%CI)	IPMN (n = 19)	P; OR (95%CI)
-511 C/T							
CC	44	35	1	13	1	6	1
CT	47	44	0.64; 1.18 (0.64-2.16)	31	0.04; 2.23 (1.04-4.81)	10	0.59; 1.56 (0.52-4.65)
TT	7	6	1; 1.08 (0.33-3.49)	7	0.04; 3.95 (1.13-13.84)	3	0.16; 3.14 (0.64-15.56)
CT + TT	54	50	0.37; 1.36 (0.75-2.44)	38	0.02; 2.38 (1.13-5.02)	13	0.32; 1.76 (0.62-5.03)
C allele	135	114	1	57	1	22	1
T allele	61	56	0.74; 1.09 (0.7-1.69)	45	0.03; 1.75 (1.07-2.86)	16	0.19; 1.61 (0.79-3.28)
+3954 C/T							
CC	45	50	1	33	1	8	1
CT	44	28	0.08; 0.57 (0.31-1.07)	16	0.07; 0.49 (0.24-1.03)	10	0.79; 1.28 (0.46-3.54)
TT	9	7	0.59; 0.7 (0.24-2.04)	2	0.19; 0.3 (0.06-1.49)	1	1; 0.62 (0.07-5.64)
CT + TT	53	35	0.1; 0.59 (0.33-1.07)	18	0.04; 0.46 (0.23-0.93)	11	0.81; 1.18 (0.43-3.15)
C allele	134	128	1	82	1	26	1
T allele	62	42	0.16; 0.71 (0.45-1.12)	20	0.03; 0.53 (0.29-0.94)	12	0.85; 1.07 (0.51-2.25)

pNET: Pancreatic neuroendocrine tumor; PDAC: Pancreatic adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasm.

allele seems to have a protective role in the pNET development since it is found to be over-represented in healthy controls. The haplotype analysis did not reveal any significant association. No significant association was found between genotypes, haplotypes, and clinicopathological data of the patients.

DISCUSSION

PNETs are a rare, heterogeneous group of neuroendocrine tumors. They usually have a better prognosis than the PDACs. The cause of these tumors is not fully understood, but differential expression of proinflammatory cytokines were found in pNET tissues[19-21]. The findings of this study suggested a possible role of *IL-1β* -511 C/T genotypes in the pathogenesis of pNETs since the presence of the *IL-1β* -511 CT and TT genotypes and the T allele was associated with an increased risk of pNET only. None significant correlation was found with PDAC and IPMN cases. Although Barber *et al*[36], reported that the +3954 C/T polymorphism of the *IL-1β* gene predisposes to pancreatic cancer; our findings did not reveal any significant association. Additionally, they are partly in agreement with the findings of Cigrovski Berkovic *et al*[37], which suggest that there is an association between the *IL-1β* -511 C/T genotype and the susceptibility to pNET, especially functional pNETs. In our study we did not find any haplotype combination to be statistically associated with the susceptibility to pNETs, neither PDAC nor IMPN cases, but we observed that the +3954T allele is over-represented among healthy controls compared to pNET cases suggesting that this allele might have a protective role in pNET development.

Carcinogenesis in the gastrointestinal tract and pancreas is often associated with chronic inflammation[39-42]. It is known that the carriers of the -511T allele associated with high IL-1β serum levels[38], and in different type of cancers IL-1β levels correlate with inflammation, worse prognosis and carcinoembrional antigen (CEA) levels, a well-known biomarker of tumor exocrine differentiation[25,43].

Our previous results suggested that *TNF-α* -1031 polymorphism is associated with the development of pNET and IPMN[41], and several studies supported that pro-inflammatory cytokines were detected in pNET tissues signifying their etiological involvement[19,44]. Taken these into consideration future studies in larger populations are needed to elucidate the role of cytokines and inflammatory pathway in the sporadic pNET development.

COMMENTS

Background

Carcinogenesis in the gastrointestinal tract and pancreas is often associated with chronic inflammation. The study provides evidence of a role of interleukin 1β (*IL-1β*) -511 C/T genotypes in the pathogenesis of pancreatic neuroendocrine tumors (pNETs).

Research frontiers

PNETs are a rare, heterogeneous group of neuroendocrine tumors. They usually have a better prognosis than the pancreatic adenocarcinomas. The cause of these tumors is not fully understood, but differential expression of proinflammatory cytokines were found in pNET tissues. Identifying genetic factors associated basically with pNET incidence may help in the primary prevention of pNET across the globe.

Innovations and breakthroughs

The study suggested a possible role of *IL-1β* -511 C/T genotypes in the pathogenesis of pNETs since the presence of the *IL-1β* -511 CT and TT genotypes and the T allele was associated with an increased risk of pNET only.

Applications

The study contributes to elucidate the role of cytokines and inflammatory pathway in the sporadic pNET development.

Terminology

PNETs: Pancreatic neuroendocrine tumors; PDACs: Pancreatic adenocarcinomas; IPMN: Intraductal papillary mucinous neoplasm.

Peer-review

This is an interesting study that looks at IL-1β as a potential inflammatory

cytokine stimulus for tumour formation in pNETs. While chronic inflammation is known to contribute to carcinogenesis, in the pancreas, this is peculiar to PDAC where association with chronic pancreatitis is not uncommon.

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