Association of IL-1β and IL-10 Polymorphisms with Prostate Cancer Risk and Grade of Disease in Eastern Croatian Population

Vesna Horvat[1], Sanja Mandić[1], Saška Marczi[2], Milanka Mrčela[3] and Josip Galić[4]

[1] University Hospital Centre Osijek, Department of Clinical Laboratory Diagnostics, Osijek, Croatia

[2] University Hospital Centre Osijek, Clinical Institute of Nuclear Medicine and Radiation Protection, Department of Molecular Diagnostics and Tissue Typing, Osijek, Croatia

[3] University Hospital Centre Osijek, Institute for Pathology and Forensics Medicine, Osijek, Croatia

[4] University Hospital Centre Osijek, Department of Urology, Osijek, Croatia

ABSTRACT

Single nucleotide polymorphisms (SNPs) in the promotor regions of cytokine genes included in angiogenesis may influence prostate cancer (PCa) development via regulation of the pathways of tumor angiogenesis. The aim of the present study was to investigate the association of IL-1♀+3954 (rs1143634) and IL-10-1082 (rs1800896) polymorphisms with PCa risk and aggressiveness in eastern Croatian patients. One hundred twenty PCa patients and 120 benign prostatic hyperplasia (BPH) controls were genotyped using real-time PCR (LightCycler Instrument, Roche Diagnostics) and the melting curve analysis method. There was no significant difference in the frequency of genotypes for the two polymorphisms between PCa patients and controls ($\chi^2=0.857$, $p=0.355$ for IL-♀1; $\chi^2=0.026$, $p=0.872$ for IL-10). Carriers of the IL-10-1082A>G variant were found to be associated with the Gleason score (GS)>7 (AA versus GA+GG, OR=3.47, 95% CI 1.11–10.88, p=0.033). There was no significant difference in the frequency of genotypes for the two polymorphisms and the presence of metastatic disease in PCa patients. These results suggest that tested SNPs associated with differential production of IL-1♀ and IL-10 are not risk factors for PCa and do not correlate with the presence of distant metastasis in eastern Croatians. We found that IL-10-1082 GA+/or GG carriers have a higher risk of developing PCa with GS>7 in eastern Croatians.

Key words: prostate cancer, benign prostatic hyperplasia, Gleason score, angiogenesis, SNP, interleukin-1♀, interleukin-10, eastern Croatia, risk, grade

Introduction

It is well known that the risk of cancer and subsequent neoplastic events (tumor growth, invasion, metastatic spread, response to therapy and survival) are strongly affected by factors predetermined by the individual's genetic background[1]. There are also, an increasing amount of evidence that supports the importance of the genetic role in the etiology of prostate cancer (PCa)[2–4]. Studies on twins suggest that up to 50% risk of PC can be explained by genetic factors[1,5].

PCa is the most common non-skin cancer among men in the USA and the EU[6–8]. In Croatia, PCa is in second place (following lung cancer) and in third place according to mortality[9].

Like other solid tumors, PCa is dependent on angiogenesis[10] e.g. the ability to create new blood vessels which support its growth and allow penetration into the surrounding tissues and metastatic spread[11]. Among others, the angiogenic factors include cytokines, which are known to have a key role in the regulation of humoral and cellular immune responses and play a role in the malignant process[12]. They have a direct effect on the growth inhibition of tumor cells, lead to tumor regression, enhance antitumor immune effects, act as growth factors for tumor cells and can mediate paraneoplastic effects[13].

Interleukin-1 (IL-1) is a pro-inflammatory and pro-angiogenic cytokine, primarily secreted by monocytes and

macrophages. IL-1 family is composed of two glycoprotein IL-1α and IL-1β and IL-1 receptor antagonist (IL-1Ra)[14]. IL-1β acts on angiogenesis by direct action on vascular endothelial cells or by enhancing production of pro-angiogenic factors via paracrine control. Together with IL-6 it stimulates angiogenesis and the production of the vascular endothelial growth factor (VEGF) in the cells of the cancer, and in glioma cells[15]. An antagonist of IL-1β receptor inhibits angiogenesis and tumor growth, suggesting that the signalling through the IL-1β receptors is involved in inflammation and tumor growth. Song et al. reported that IL-1β promotes tumor invasiveness, angiogenesis and suppresses the host immune system[16]. Experimental studies have shown the association of IL-1β with PCa[17]. Regions of cytokine genes contain polymorphisms that directly influence cytokine production. These single nucleotide polymorphisms (SNPs) are associated with different levels of cytokine production and may cause interindividual differences and thus influence antitumor immune responses[18–20]. SNPs in the IL-1β gene on chromosome 2q14 are associated with increased production of IL-1β and increased risk of various types of cancer[21–23]. The most common examined polymorphisms are −511C>T in the promoter region and +3954C>T in exon 5 on IL-1β gene[18,20,24–27].

Interleukin-10 (IL-10) is anti-inflammatory and anti-angiogenic cytokine secreted primarily by macrophages and T-lymphocytes. It seems that the effect of IL-10 on macrophages affect the regulation of angiogenesis in various cancers[28–30], and its immunosuppressive and anti-inflammatory properties contribute to the growth of the tumor, enabling them to avoid immune responses. However, animal and in vitro studies have shown that a high value of IL-10 reduces tumor growth and angiogenesis[31]. SNPs in the IL-10 gene on chromosome 1 (1q31–1q32) lowers the production of IL-10 and increases cancer risk (cancer of the cervix, stomach, kidney, melanoma)[32–34]. The most commonly studied polymorphisms are the −1082A>G, −592C>A, −819C>T in the promoter region of IL-10 gene[19,27,35–37].

Although the results of the genetic variations of IL-1β and IL-10 and the association with cancer are contradictory, animal studies and in vitro models support the hypothesis of an association between a high production of IL-1β and a low production of IL-10 cytokines with tumori genesis in the prostate.

The aim of this case-control study was to evaluate the association between the IL-1β+3954C>T and IL-10-1082A>G polymorphisms with the risk and aggressiveness of PCa in the eastern Croatian population.

Materials and Methods

Subjects

A total of 240 subjects from eastern Croatia were included in the prospective, case-control study, 120 PCa patients and 120 benign prostatic hyperplasia (BPH) patients. They all were treated in the period of 2008–2010 at the Department of Urology, University Hospital Centre Osijek.

PCa and BPH patients had a digital rectal examination (DRE) and a serum prostate specific antigen (PSA) concentration determination. All patients with an elevated PSA concentration (>4ng/mL) and/or suspicious DRE were included in the study and they all underwent transrectal ultrasound (TRUS) guided 12-core needle prostate biopsy. One hundred twenty patients had histological confirmation of PCa while another 120 patients had histological confirmed BPH and therefore they represented controls. PCa patients were classified according to their Gleason score (GS) in a less and moderately aggressive form with GS≤7 and a highly aggressive form with GS>7. According to the results of bone scintigraphy and computed tomografy (CT) they also, were classified as M0-no metastasis and M1-with metastasis. Groups were age matched. Subjects who had normal DRE and PSA<4 ng/mL, or those with some other site of cancer were excluded from the study.

Before DRE and blood sampling each participant completed a pre-designed questionnaire with information regarding age, smoking status, alcohol consumption, associated medical history etc. (Table 1). A written informed consent was obtained from each participant.

The study was approved by the Ethics Committee of University Hospital Centre Osijek and Ministry of Science, Education and Sports of the Republic of Croatia.

Blood sampling

Blood samples for each participant were collected by a puncture from an antecubital vein in serum separator tubes (BD Vacutainer, Becton Dickinson, Plymouth, UK) for PSA determination and K_2EDTA tubes (BD Vacutainer, Becton Dickinson, Plymouth, UK) for analysing polymorphisms of interest.

Genotyping of the IL-1β (rs1143634) and IL-10 (rs1800896)

Genomic DNA was extracted from 200 µL of peripheral blood samples by standard procedure using the High Pure PCR Template Preparation Kit (Roche, Mannheim, Germany). Real-time PCR and melting curve analysis were performed on LightCycler 1.5 Instrument (Roche, Mannheim, Germany). The PCR primers were synthesized by Invitrogen (Paisley, UK) and fluorescent-labelled probes by TIB MOLBIOL (Berlin, Germany).

Genotyping of the IL-1β+3954 SNP was performed as previously described in Palli et al[35]. Briefly, a total reaction volume of 10 µL contained of 1.5 µL of sample DNA, 1x LC DNA Master Hybridization Probes Mix (Roche, Mannheim, Germany), 3.0 mM $MgCl_2$, 0.5 µM primers each (5'-GTT GTC ATC AGA CTT TGA CC-3' and 5'-TTC AGT TCA TAT GGA CCA GA-3') and 0.15 µM hybridization probes each (5'-CCT ATC TTC TTC GAC ACA TGG

G-FL-3' and 5'-LCRed640-ACG AGG CTT ATG TGC ACG ATG C-P-3'). The PCR program consisted of initial denaturation (10 min at 95°C), amplification (30 cycles: 10s at 97°C, 10s at 63°C, 10s at 72°C, 35 cycles: 10s at 95°C, 10s at 58°C, 10s at 72°C) and melting curve acquisition (40°C to 80°C with temperature transition of 0.1 °C/s). Melting temperatures of allele C and allele T were 63°C and 55°C, respectively.

Genotyping of the IL-10-1082 polymorphism was performed according to Timmann et al.[36] with minor modifications. Briefly, 2 µL of sample DNA were placed in a total volume of 10 µL of reaction solution also containing 1x LC DNA Master Hybridization Probes Mix (Roche, Man-

nheim, Germany), 4.0 mM $MgCl_2$, 1.0 µM 5'-ATC CAA GAC AAC ACT ACT AAG GC-3' primer, 0.5 µM 5'-GGG TGG GCT AAA TAT CCT CAA-3' primer, 0.2 µM probes each (5'-GGA TAG GAG GTC CCT TAC TTT CCT CTT ACC-FL-3' and 5'-LCRed640-CCC TAC TTC CCC CTC CCA AA-P-3') and 0.5 µL DMSO (final concentration 5%). The cycling program consisted of initial denaturation (30s at 94°C), amplification (50 cycles: 5s at 94°C, 15s at 50°C, 20s at 72°C) and melting curve acquisition (42°C to 78°C with temperature transition of 0.1 °C/s). In these conditions melting temperatures of allele G and allele A were 62.5°C and 53°C, respectively.

Statistical analysis

The Man-Whitney rank sum test was used to compare demographic and clinical characteristics between cases and controls. Allele frequencies were estimated and tested for fit to the expectations of Hardy-Weinberg equilibrium (HWE). Genotype and allele frequencies between cases and controls and among GS and metastasis subgroups of PCa were compared by Chi-square (χ^2) statistics or Fischer's exact tests. Relative risk was estimated by the odds ratio (OR) and 95% confidence interval (CI). The difference was considered statistically significant when p<0.05. Statistical analyses were performed using MedCalc for Windows, version 12.4.0.0 (MedCalc Software, Mariakerke, Belgium).

Results

Basic clinical and demographic characteristics of PCa patients and BPH controls with corresponding p values are shown in Table 1. The groups did not differ in age or hereditary PCa incidence. There was a difference in the number of smokers between the groups, although not statistically significant. The number of obese people (BMI>30) was significantly higher in the PCa group. There was a statistically significant difference in PSA values between the PCa and BPH group (p=<0.001) with the interquartile range (IQR) significantly higher in the PCa group. The BPH group has higher TRUS-assessed prostate volume values than the PCa patients. Among PCa patients, 23.7% had a GS>7 and 33.9% had distance metastases. Two patients did not have data about GS and M status and were not included in the statistical analysis. The distribution of genotypes for each SNP in the PCa and control group was in agreement with HWE.

Table 2 shows clinical and demographic characteristics of PCa patients with GS≤7 and GS>7 with corresponding p values. There was a statistically significant difference in PSA values and the presence of distant metastasis between these groups (p=<0.001).

Comparison of genotypes and allele frequencies of IL-1ß+3954C>T and IL-10-1082A>G polymorphisms and corresponding OR for PCa risk are shown in Table 3. There was no significant difference in the frequency of genotypes for the two polymorphisms between PCa patients and con-

TABLE 1
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY SUBJECTS

	PCa (N=120) N (%)	BPH (N=120) N (%)	p value*
Age categories			
<50	3 (2.5)	3 (2.5)	
50–59	18 (15.0)	13 (10.8)	
60–69	48 (40.0)	54 (45.0)	
70–79	46 (38.3)	50 (41.7)	
≥80	5 (4.2)	0 (0)	
($\overline{X}$±SD)	67.5±7.8	67.6±6.6	0.961
Smoking status			
Nonsmoking	70 (58.3)	88 (73.3)	
Smoking	50 (41.2)	32 (26.7)	0.068
History of prostate cancer			
No	110 (91.7)	113 (94.2)	
Yes	10 (8.3)	7 (5.8)	0.463
PSA (ng/mL)			
≤10	46 (38.3)	29 (24.2)	
>10	74 (61.7)	91 (75.8)	
Median (IQR)	12.4 (6.7–35.1)	6.81 (5.1–9.5)	<0.001
Body Mass Indeks (kg/m²)			
<25	27 (22.9)	34 (29.1)	
25–30	57 (48.3)	66 (56.4)	
>30	34 (28.8)	17 (14.5)	0.019
Gleason score			
≤7	90 (76.3)		
>7	28 (23.7)		
Distant metastasis			
M0	78 (66.1)		
M1	40 (33.9)		

* p value of Mann-Whitney rank sum test, PCa – prostate carcinoma, BPH – benign prostatic hyperplasia, IQR-interquartile range

TABLE 2
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PCa PATIENTS

	GS≤7 (N=90) N (%)	GS>7 (N=28) N (%)	p value*
Age categories (%)			
< 50	1 (1.1)	1 (3.6)	
50–59	17 (18.9)	2 (7.1)	
60–69	39 (43.3)	9 (32.1)	
70–79	31 (34.4)	14 (50.0)	
≥ 80	2 (2.2)	2 (7.1)	
($\overline{X}$±SD)	66.5 ± 7.4	70.3 ± 7.9	0.009
Smoking status			
Nonsmoking	55 (61.1)	16 (59.3)	0.871
Smoking	35 (38.9)	11 (40.7)	
History of prostate cancer			
No	81 (90.0)	27 (96.4)	
Yes	9 (10.0)	1 (3.6)	0.291
PSA (ng/mL)			
≤10	41 (45.6)	4 (14.3)	
>10	49 (54.4)	24 (85.7)	
Median (IQR)	10.4 (6.1–22.4)	33.9 (17.9–178.1)	<0.001
Body Mass Indeks (kg/m²)			
<25	17 (19.1)	10 (37.0)	
25–30	44 (49.4)	12 (44.4)	
>30	28 (31.5)	5 (18.5)	0.040
Distant metastasis			
M0	69 (76.7)	9 (32.1)	
M1	21 (23.3)	19 (67.9)	<0.001

* p value of Mann-Whitney test, not including missing values in all variables, GS-Gleason score, IQR-interquartile range

trols (χ²=0.857, p=0.355 for IL-β1; χ²=0.026, p=0.872 for IL-10).

In patients with PCa we made a linkage analysis of selected IL-1β and IL-10 SNPs with GS and the presence of distant metastases.

Table 4 shows a comparison of genotypes and allele frequencies of IL-1β+3954C>T and IL-10-1082A>G with GS in patients with PCa. There was no statistically significant difference in the frequency of IL-1β genotypes and alleles between PCa patients by GS. IL-10-1082G allele polymorphism frequency was higher in PCa patients with GS>7, although not statistically significant. IL-10-1082 GA+/or GG genotype showed 3.47 times higher risk for PCa with GS>7.

Table 5 shows a comparison of genotype frequencies for IL-1β+3954C>T and IL-10-1082A>G due to the presence of distant metastases in patients with PCa. There was no statistical difference in the frequency of genotypes for IL-1β and IL-10 polymorphisms and any correlation between the frequencies of these two polymorphisms and the presence of metastatic disease in PCa patients.

In addition, there were 14 wild type (IL-1β+3954CC/IL-10-1082AA) double homozygotes in both groups, 24 double heterozygotes (IL-1β+3954CT/IL-10-1082AG) in the BPH group and 32 in the PCa group, 1 mutant form double homozygote (IL-1β+3954TT/IL-10-1082GG) in the BPH group and 5 in the PCa group.

Discussion

The association of IL-1β+3954 and IL-10-1082 polymorphisms with PCa risk and aggressiveness were investigated in this prospective study, in eastern Croatian patients. Carriers of the IL-10-1082A>G variant were found to be associated with the GS>7 and IL-10-1082 GA+/or GG genotype showed 3.47 times higher risk for PCa with GS>7. No significant difference was found in the frequency of genotypes for the two polymorphisms between PCa patients and controls. Also, there was no significant difference in the frequency of genotypes for the two polymorphisms and the presence of metastatic disease in PCa patients.

PCa is like other types of cancer, an actively progressive disease. It is imperative to establish mechanisms to identify people who are at risk of developing a more aggressive form of PCa. Interindividual genetic variations can influence the interaction between cancer cells and hormones, growth factors, and the factors that influence tumor microenvironment, thus they may greatly contribute to the risk, aggressiveness, treatment outcome and prognosis of cancer.

Angiogenesis has an important part in many human malignancies including PCa. Cytokines, which have a key role in the regulation of humoral and cellular immune response and play a role in the malignant process, are also angiogenic factors. Polymorphisms in regions of cytokine genes directly influence cytokine production so they may influence PCa development via regulation of the antitumor immune response and/or pathways of tumor angiogenesis.

Angiogenic molecular epidemiological studies in PCa, suggested the possibility of predicting susceptibility and prognosis by analyzing genetic polymorphisms[19].

In this study, we examined SNPs of two cytokines IL-1β+3954 and IL-10-1082. They were selected because they have been reported to influence expression of their respective cytokine *in vitro*[38]. Therefore, we proposed that changes in expression of these two cytokines may influence the process of angiogenesis.

Zabaleta et al. first studied patients with gastric premalignant lesions and showed an association of development of multifocal atrophic gastritis with the presence of IL-1β+3954T allele[39]. They proposed allele IL-1β+3954T

TABLE 3

CYTOKINE GENOTYPE AND ALLELE FREQUENCIES FOR PROSTATE CANCER RISK AMONG STUDY PARTICIPANTS

SNP	Variant	PCa N (%)	BPH N (%)	OR (95%CI)	p
IL-1ß+3954	CC	43 (35.8)	51 (42.5)	1.00	
	CT	60 (50.0)	59 (49.2)	1.21 (0.70–2.07)	0.498
	TT	17 (14.2)	10 (8.3)	2.02 (0.84–4.86)	0.118
	CT+TT	77 (64.2)	69 (57.5)	1.32 (0.79–2.22)	0.290
	C allele	146 (60.8)	161 (67.1)	1.00	
	T allele	94 (39.2)	79 (32.9)	1.31 (0.90–1.91)	0.154
IL-10-1082	AA	37 (30.8)	42 (35.0)	1.00	
	GA	59 (49.2)	54 (45.0)	1.24 (0.70–2.20)	0.464
	GG	24 (20.0)	24 (20.0)	1.13 (0.55–2.33)	0.729
	GA+GG	83 (69.2)	78 (65.0)	1.21 (0.70–2.07)	0.492
	A allele	133 (55.4)	138 (57.5)	1.00	
	G allele	107 (44.6)	102 (42.5)	1.09 (0.76–1.56)	0.645

SNP – single nucleotide polymorphism, PCa – prostate carcinoma, BPH – benign prostatic hyperplasia, OR – odds ratio

TABLE 4

ASSOCIATION OF IL-1ß AND IL-10 POLYMORPHISMS ACORRDING TO LEVEL OF PCa DIFFERENTIATION (GLEASON SCORE)

SNP	Variant	GS≤7 N (%)	GS>7 N (%)	OR (95%CI)	p
IL-1ß+3954	CC	33 (36.7)	9 (32.1)	1.00	
	CT	44 (48.9)	16 (57.1)	1.33 (0.52–3,39)	0.546
	TT	13 (14.4)	3 (10.7)	0.85 (0.20–3.63)	0.822
	CT+TT	57 (63.33)	19 (67.9)	1.22 (0.50–3.01)	0.663
	C allele	110 (61.1)	34 (60.7)	1.00	
	T allele	70 (38.9)	22 (39.3)	1.02 (0.55–1.88)	0.958
IL-10-1082	AA	33 (36.7)	4 (14.3)	1.00	
	GA	40 (44.4)	17 (60.7)	3.51 (1.07–11.44)	0.038
	GG	17 (18.9)	7 (25.0)	3.40 (0.87–13.24)	0.078
	GA+GG	57 (63.3)	24 (85.7)	3.47 (1.11–10.88)	0.033
	A allele	106 (58.9)	25 (44.6)	1.00	
	G allele	74 (41.1)	31 (55.4)	1.78 (0.97–0.25)	0.063

SNP – single nucleotide polymorphism, GS – Gleason score, OR – odds ratio

as a marker for those individuals who do not advance to more aggressive stage of the disease, since only a minor fraction of patients with multifocal atrophic gastritis progress to dysplasia and to gastric cancer. Afterward, they hypothesized if there is a correlation of IL-1β+3954 polymorphism with PCa risk and aggressiveness. They found, on the contrary that Caucasian-American individuals carrying IL-1β+3954TT genotype had a >3-fold risk of being diagnosed with aggressive PCa[25] but there was

no association with PCa risk[40]. Michaud et al.[27] in the Prostate, Lung, Colorectal and Ovarian (PLCO) Screening trial with 1320 PCa cases (1213-White males, 107-Black males) and 1842 controls (1443-White males, 409-Black males) found no associations with the risk and aggressiveness of PCa with IL-1β+3954TT genotype. Our results show no association of IL-1β+3954TT genotype with aggressiveness of PCa or the presence of distant metastasis. We found a slight increase in the risk of PCa with

TABLE 5

ASSOCIATION OF IL-1ß AND IL-10 POLYMORPHISMS ACCORDING THE PRESENCE OF DISTANT METASTASIS

SNP	Variant	M0 N (%)	M1 N (%)	OR (95%CI)	p
IL-1ß+3954	CC	26 (33.3)	16 (40.0)	1.00	
	CT	40 (51.3)	19 (47.5)	0.77 (0.34–1.77)	0.540
	TT	12 (15.4)	5 (12.5)	0.68 (0.20–2.28)	0.529
	CT+TT	52 (66.7)	24 (60.0)	0.75 (0.34–1.65)	0.475
	C allele	92 (59.0)	51 (63.8)	1.00	
	T allele	64 (41.0)	29 (36.2)	0.82 (0.47–1.42)	0.477
IL-10-1082	AA	26 (33.3)	10 (25.0)	1.00	
	GA	37 (47.4)	21 (52.5)	1.47 (0.60–3.65)	0.399
	GG	15 (19.2)	9 (22.5)	1.56 (0.52–4.70)	0.429
	GA+GG	52 (66.7)	30 (75.0)	1.50 (0.64–3.53)	0.354
	A allele	89 (57.1)	41 (51.2)	1.00	
	G allele	67 (42.9)	39 (48.8)	1.26 (0.73–2.17)	0.398

SNP – single nucleotide polymorphism, M – distant metastasis, OR – odds ratio

IL-1β+3954T allele, although it was not statistically significant (p=0.118).

In our study there was no statistically significant difference in the frequency of IL-10-1082 genotypes and alleles between PCa patients and controls. However, after comparing low/intermediate PCa grades with high-grade PC, we found that the risk of developing aggressive PCa tends to increase in patients with G allele, but without statistical significance. IL-10-1082 GA and GG genotype carriers showed a 3.47-fold higher risk of developing PCa with GS>7. These results are partially in agreement with the study by Zabaleta et al.[25]. They found that IL-10-1082GG genotype which correlate with high IL-10 production, is not only associated with aggressive PCa disease but also with PCa risk. Nevertheless, we did not find an association of IL-10-1082GG genotype with the presence of distant metastasis.

Conversely, McCarron et al.[19] or Kesarwani et al.[26] observed a significant positive association between IL-10-1082AA genotype with low IL-10 production and increased odds ratio of developing PCa.

Neither Michaud et al.[27] nor Eder et al.[36] report any correlation between IL-10 expression and PCa risk status.

The cause of these differences remains unclear. It is not clear how IL-10 may play a dual role in the development of malignancy. By suppressing the Th1 response and by inhibiting phagocytic functions, IL-10 may promote tumor cells to evade the immune system and promote uncontrolled metastasis. In contrast, higher levels of IL-10 have been associated with reduced angiogenesis via reduction of VEGF expression[29], controlling the progression of the tumor by limiting access to the blood supply.

The lack of consistency of single SNP analysis in PCa susceptibility and aggressiveness may be due to several possibilities: the relatively minor effect that a single SNP may have in the expression or function of the gene, genetic trait differences, the existence of distinct genetic polymorphisms among specific populations, ethnicities and geographic regions. Moreover as cancer is a multifactorial disease, individual exposures to various environmental factors (smoking, environment exposures, inflammation, viral infections and others) in combination with genetic susceptibility may have contributed to these varied results.

Due to the small number of double homozygotes and double heterozygotes in subgroups and low power of testing, these comparisons have not been included in the study.

In summary, our results suggest that IL-1β+3954 polymorphism might not be risk factor of PCa development and aggressiveness. However, IL-10-1082- AG and GG genotypes may impact PCa aggressiveness in Croatians. Since angiogenic genes polymorphisms may affect disease outcomes, treatment responses and immunotherapy, further target studies on the effects of SNPs are required to understand genetic susceptibility to PCa.

Acknowledgements

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V. Horvat

University Hospital Centre Osijek, Department of Clinical Laboratory Diagnostics, J. Huttlera 4, 31000 Osijek,Croatia
e-mail: horvat.vesna@gmail.com

POVEZANOST IL-1β I IL-10 POLIMORFIZAMA S RIZIKOM I PROGRESIJOM RAKA PROSTATE U POPULACIJI ISTOČNE HRVATSKE

SAŽETAK

Pojedinačni nuklearni polimorfizmi (SNP) u promotorskim regijama gena citokina uključenih u angiogenezu, mogu utjecati na razvoj karcinoma prostate (PCa) regulacijom putova angiogeneze tumora. Cilj ove studije bio je istražiti povezanost IL-1β+3954 (rs1143634) i IL-10-1082 (rs1800896) polimorfizama s rizikom i agresivnošću karcinoma prostate kod pacijenata iz istočne Hrvatske. 120 pacijenata s karcinomom prostate i 120 kontrola s benignom hiperplazijom

prostate (BPH) genotipizirani su metodom lančane reakcije polimerazom u stvarnom vremenu (eng. real-time PCR) i analizom krivulje temperature taljenja pomoću tehnologije LightCycler (Roche Diagnostics). Nije bilo značajne razlike u učestalosti genotipova za dva polimorfizma između PCa bolesnika i kontrola (χ^2=0,857, p=0,355 za IL-β1; χ^2=0,026, p=0,872 za IL-10). Utvrđena je povezanost nosioca IL-10-1082A>G varijante s GS>7 (AA u odnosu na GA+GG, OR=3,47; 95% CI 1.11 do 10,88, p=0,033). Nije bilo značajne razlike u učestalosti genotipova za dva polimorfizma i prisutnosti metastatske bolesti u PCa bolesnika. Ovi rezultati sugeriraju da testirani SNP-ovi, povezani s različitom produkcijom IL-1β i IL-10, nisu čimbenici rizika za PCa i ne koreliraju s prisutnošću metastaza kod ispitanika u istočnoj Hrvatskoj. Otkrili smo da u istočnoj Hrvatskoj, nositelji IL-10-1082 GA +/ili GG genotipa imaju veći rizik razvoja PCa s GS>7.