Heterozygosity for Interleukin-18 –607 A/C Polymorphism is Associated with Risk for Colorectal Cancer

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Abstract. *Background: The possible contribution of interleukin-18 (IL-18) –607 A/C polymorphism towards the development of colorectal cancer was investigated. Patients and Methods: DNA samples of 84 patients with colorectal cancer (adenocarcinomas) and 89 healthy controls were examined by allele-specific polymerase chain reaction followed by electrophoretic analysis. The resulting allele and genotype frequencies of patients were compared to those of the respective controls using Fischer's exact test and odds ratios. Results: The proportion of heterozygotes in the patient group was significantly higher than that in healthy controls ($p<0.01$). This significant increase was detected independently of Dukes' tumor stage. Additionally, the carrier frequency of the mutant A allele was significantly higher in the patient group compared to controls ($p<0.05$). Conclusion: The results indicate that heterozygotes for the IL-18 –607 A/C polymorphism exhibit increased risk for colorectal cancer development.*

Colorectal carcinoma (CRC) is one of the most common malignancies worldwide, as it accounts for 9.4% of total cancers cases, while it ranks fourth in frequency in men and third in women (1). Genetic factors, such as alterations in oncogenes and tumor suppressor genes, as well as other factors, including diet, smoking, drugs or poor hygiene, have been linked to the pathogenesis of the disease (2-4). Hereditary syndromes, with autosomal dominant or recessive inheritance, account only for about 2-6% of the cases, suggesting that the majority of colorectal malignancies do not have a recognizable inherited cause (4). Recently, subtle DNA alterations in low penetrance genes have emerged as important determinants of susceptibility to cancer through genetic association studies (5). Such studies have revealed an association between a considerable number of factors involved in angiogenesis, inflammation and thrombosis with increased risk for several types of cancer (6-27). Interleukin-18 (IL-18) is one such factor, previously correlated to angiogenesis, inflammation and cancer (28-30).

IL-18, also known as interferon-γ inducing factor, is a pleiotropic pro-inflammatory cytokine, a member of the IL-1 superfamily, with a key role in driving the Th1 pro-inflammatory response (31, 32). It has been proposed that IL-18 modulates the immune system for attacking cancer cells through the suppression of tumor growth and angiogenesis in ovarian cancer, inhibition of breast cancer cell proliferation and potential invasion and also through the enhancement of cytotoxic effects on colon carcinoma cells (33-35). Furthermore, increased levels of IL-18 have been reported in head and neck squamous cell carcinoma, esophageal, gastric, ovarian, colon, skin, hepatocellular and myeloid leukemia cells (33, 36-42).

Two functional single nucleotide polymorphisms (SNPs) in the promoter region of the *IL-18* gene seem to modulate gene expression at the transcriptional level (15). Tight linkage disequilibrium exists between these two SNPs (15). One of them, located at position –607, involves a C to A substitution alterating a cAMP-responsible element binding site, resulting in a decrease of transcription (15, 43). The frequency of the low transcription A allele ranges between 34-42% in Caucasians and 44-53% in Asians (44-47).

The purpose of this study was to examine whether there is any association between the –607 C/A polymorphism in the *IL-18* gene and colorectal cancer by investigating the prevalence of its genotypes, allele and carrier frequencies in patients with CRC and matched healthy controls.

Patients and Methods

In this study, 173 individuals of Greek origin were enrolled, including 84 patients surgically treated for colorectal cancer (adenocarcinomas) within the last 5 years and 89 healthy blood donors. DNA extraction was performed from biopsies of patients

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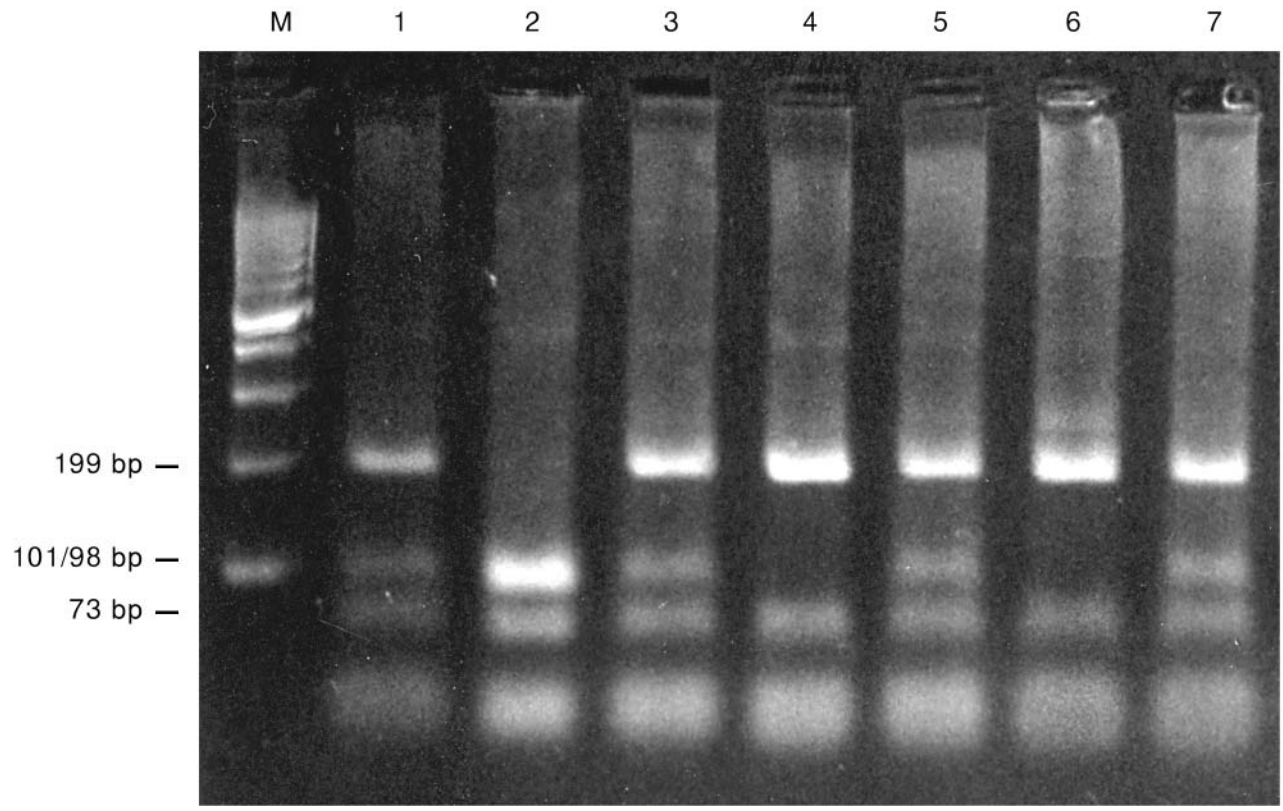

Figure 1. *An illustrative example of observed –607A/C IL-18 genotypes in 7 patients with colorectal cancer, after agarose gel electrophoresis of MseI-digested PCR products. The C allele corresponds to three fragments of 29, 73 and 199 bp, while the A allele to four fragments of 29, 73, 98 and 101 bp. The common 29 bp fragment is lost within the visible band of the primers. M: molecular weight marker; 1, 3, 5, 7: AC heterozygotes; 2: AA homozygote; 4, 6: CC homozygotes.*

and from blood samples of controls. The biopsies were characterized pathologically and in regard to cancer stage, according to Dukes's stage. Molecular detection was performed by restriction fragment length polymorphism analysis of polymerase chain reaction products and gel electrophoretic analysis (Figure 1), as described elsewhere (48). The frequencies of alleles and genotypes in patients were compared to the respective frequencies of the control group and bilateral statistical analysis was performed using Fisher's exact test, with the level of significance set at $p<0.05$. Age-adjusted odds ratios were calculated using the Mantel-Haenszel method with a 95% confidence interval (CI), while the age criterion for the adjustment of odds ratios was set at 55 years. The genotypes in the control group were checked for compliance with the Hardy-Weinberg equilibrium.

Results

The prevalence of the detected *IL-18* genotypes, A allele and carrier frequencies observed in healthy controls, patients, and patients grouped according to Dukes's stages A, B (early) and C, D (advanced) are shown in Table I. In the control group, the genotypes were in Hardy-Weinberg equilibrium.

The detected genotypes of the *IL-18* –607A/C polymorphism revealed a statistically significant increase in the number of AC heterozygotes in patient group overall and in the subgroups of patients with cancer in early stages (Dukes' stages A, B) and in advanced stages (C, D), when compared with the healthy control group ($p=0.008$, $p=0.02$ and $p=0.05$ respectively). AC heterozygotes seem to have an approximately three-fold greater risk (odds ratio, OR) of developing CRC than do CC homozygotes (OR=3.05, 95% CI 1.42-6.56).

Furthermore, the carrier frequency of the mutant A allele was significantly higher in the patient group in comparison to the control group ($p=0.02$). Finally, there was no statistical difference in the frequencies of the two *IL-18* alleles due to categorization of gender, age or cancer stage (early *versus* advanced).

Discussion

Only one previous association study of the *IL-18* –607 A/C polymorphism with malignancy has been reported, which detected no association of this specific polymorphism with oral cancer (48). IL-18 expression has been previously investigated in several types of cancer, including gastric and

Table I. *Prevalence of IL-18 –607A/C polymorphism in healthy controls, colorectal cancer patients, and patients grouped according to Dukes' stages A, B and C, D.*

	Controls	Patients			Patients with cancer stages A,B			Patients with cancer stages C,D		
Genotypes	(N %)	(N %)	Fisher's *p*-value	OR (CI)	(N%)	Fisher's *p*-value	OR (CI)	(N%)	Fisher's *p*-value	OR (CI)
Mutant AA	22 (24.7%)	18 (1.4%)	0.40	1.54 (0.62-3.81)	7 (17.1%)	0.78	1.34 (0.40-4.55)	11 (25.6%)	0.31	1.73 (0.61-4.89)
Normal CC	35 (39.3%)	19 (22.6%)		1 (referent)	9 (22%)		1 (referent)	10 (23.3%)		1 (referent)
Carrier AC	32 (36%)	47 (56%)	**0.008**	3.05 (1.42-6.56)	25 (60.9%)	**0.02**	3.39 (1.32-8.75)	22 (51.1%)	**0.05**	2.60 (1.01-6.74)
Total	89 (100%)	84 (100%)			41 (100%)			43 (100%)		
Prevalence of A allele										
A allele frequency	42.7%	49.4%	0.24		47.6%	0.50		51.2%	0.24	
Carrier frequency of A allele	60.7%	77.4%	**0.02**		78.1%	**0.07**		76.7%	**0.08**	

Fischer's *p*-value corresponds to genotype and allele frequency comparisons; significant *p*-values are given in bold; odds ratios (OR) are age-adjusted; CI: 95% confidence interval.

colon carcinomas (30, 33-42, 48-53). In the majority of those studies, high levels of IL-18 were observed and correlated with poor prognosis and metastasis of the disease, but in certain carcinomas a correlation with tumor suppression and inhibition of angiogenesis were also seen (30, 33-42, 49-53). In colon adenocarcinomas, specifically, reduced or abolished IL-18 synthesis has been observed, suggesting that IL-18 may play a tumor-inhibiting role (35).

We studied the –607 A/C polymorphism, which affects transcription of the *IL-18* gene, in patients with CRC and healthy controls. The obtained data revealed that AC heterozygotes seem to have an increased risk for CRC, while homozygotes for the high expression C allele are more protected against this malignancy. This notion is in accordance to previous reports of reduced levels of IL-18 in colorectal carcinomas (35, 39).

Surprisingly, this study indicates that AA homozygotes, possessing twice the low expression allele, do not have a significantly increased risk for CRC. This rather paradoxical observation may imply that the AA genotype also has tumor-inhibitory properties, similar to its prophylactic role against autoimmune diseases (54, 55). It seems that stoichiometric levels of IL-18 within certain limits are necessary to disrupt the physiological effects of this cytokine in order to lead to malignancy.

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