Journal of BUON **12:** 135-136, 2007
© 2007 *Zerbinis Medical Publications. Printed in Greece*

LETTER TO THE EDITOR

Plasminogen activator inhibitor-1 gene 4G/5G polymorphism in cancer patients

Sir,

The plasminogen activator inhibitor-1 (PAI-1) is a factor in the urokinase-type plasminogen activator (uPA) proteolytic system, which plays an important role in the development of tumor invasion and metastasis. High tissue PAI-1 level is associated with a poor prognosis in a number of human cancers [1]. Although the exact mechanism by which PAI-1 influences tumor growth and dissemination remains unclear, it may promote a broad spectrum of effects in tumor biology, from the inhibition of uPA-induced proteolysis and destruction of the extracellular matrix, to the effects on cell migration and angiogenesis.

PAI-1 gene is located on chromosome 7 and contains 8 introns and 9 exons [2]. The 4G allele of 4G/5G insertion / deletion polymorphism located in the promoter region 675 bp upstream from the transcription start sequence of PAI-1 gene is responsible for the higher plasma PAI-1 level, conditioning a clear hypofibrinolytic state. Few polymorphisms have been discovered, the 4G/5G polymorphism being the most frequently studied in association with cancer. Although the studies have indicated that elevated PAI-1 level is related to poor prognosis in cancer patients, the results of recent studies on the association between the PAI-1 4G/5G polymorphism and the behavior of cancer are contradictory [3,4]. Moreover their results showed that the PAI-1 gene polymorphism did not affect cancer risk.

We have recently reported that 4G/5G polymorphism of PAI-1 gene is related to the development of breast cancer [5]. To our knowledge no investigation of the role of PAI-1 gene 4G/5G polymorphism in relation to various types of malignant tumors has been undertaken in Turkish population. To this purpose, we have conducted a study to evaluate the association between this polymorphism and various types of cancers. We enrolled two groups. The first group was composed of 125 unrelated patients with various types cancers (breast cancer in 35 patients, lung cancer in 40, digestive system cancer in 10, urogenital cancer in 5, sarcoma in 8, brain tumor in 8, lymphoma in 4, nasopharyngeal cancer in 5, and others in 10). The second group consisted of 180 unrelated healthy volunteers without history of malignancy.

Genomic DNA isolation was performed from peripheral venous blood by standard phenol-chloroform extraction, and polymerase chain reaction of the PAI-1 4G/5G polymorphism was performed as previously described [5] by using primers 5'-CACAGAGA-GAGTCTGGCCACGT-3' and 5'-CCAACAGAG-GACTCTTGGTCT-3'.

Amplification was made for 35 cycles with annealing temperature of 60° C (Biometra, Germany). Amplified 98/99-bp product was digested with Bse LI (Fermentas, Vilnius, Lithuania) at 55° C and subjected to 8% polyacrylamide gel electrophoresis.

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL). The groups were compared using chi-square test. A p-value of < 0.05 was considered statistically significant. There was a statistically significant difference in the PAI-1 gene 4G/5G polymorphism between the groups ($p=0.004$) (Table 1). There was also a significant difference in the frequency of 4G allele between cancer patients (0.628) and control subjects (0.511) ($p<0.05$). The 4G/5G polymorphism was in Hardy-Weinberg equilibrium for both the cases and controls.

Our results are controversial compared to the previous published studies showing that the distribution of the genotypes of the 4G/5G polymorphism in both patients and controls did not differ significantly [3,4]. In disagreement with the studies, carrying the PAI-1 4G allele either in heterozygous or homozygous state was found to be an increased risk of development of malignant tumor. This contrast may be explained partly by the fact that different results in different populations are due to different genetic background.

Table 1. Distribution of PAI-1 4G/5G polymorphism in patients and controls

PAI-1 gene	Patients (n=125) *n (%)*	Controls (n=180) *n (%)*
4G/4G	43 (34.4)	45 (25)
4G/5G	71 (56.8)	94 (52.2)
5G/5G	11 (8.8)	41 (22.8)
4G allele	0.628	0.511
5G allele	0.372	0.489

In summary, we found that PAI-1 4G/5G polymorphism is associated with the risk of malignant tumor development and we suggest that this polymorphism may contribute to an inherited predisposition to the development of malignancies; however further studies with larger series from diverse ethnic populations are needed to confirm our results.

References

1. Andreasen PA, Egelund R, Petersen HH. The plasminogen activation system in tumor growth, invasion, and metastasis. Cell Mol Life Sci 2000; 57: 25-40.
2. Ny T, Sawdey M, Lawrence D et al. Cloning and sequence of cDNA coding for the human beta-migrating endothelial-cell-type plasminogen activator inhibitor. Proc Natl Acad Sci USA 1986; 83: 6776-6780.
3. Smolarz B, Blasiak J, Kulig A et al. Plasminogen activator inhibitor 1 (PAI-1) levels and gene promoter polymorphisms in subjects with colorectal cancer. J Exp Clin Cancer Res 2001; 20: 247-252.
4. Castello R, Espana F, Vazquez C et al. Plasminogen activator inhibitor-1 4G/5G polymorphism in breast cancer patients and its association with tissue PAI-1 levels and tumor severity. Thromb Res 2006; 117: 487-492.
5. Eroglu A, Ulu A, Cam R, Akar N. Plasminogen activator inhibitor-1 gene polymorphism in patients with breast cancer. J BUON 2006; 11: 481-484.

A. Eroğlu[1], A. Ulu[2], R. Çam[3], N. Akar[4]

[1]Department of General Surgery and Surgical Oncology, Numune State Hospital, Konya; [2]Department of Pediatric Molecular Genetics, Ankara University Medical School, Ankara; [3]Department of General Surgery, Ankara University Medical School, Ankara; [4]Department of Pediatric Molecular Genetics, Ankara University Medical School, Ankara, Turkey

Correspondence to:

Dr. Aydan Eroğlu
Department of General Surgery and Surgical Oncology
Numune State Hospital
Konya
Turkey
E-mail: aydaneroglu@hotmail.com