A POSSIBLE ASSOCIATION BETWEEN PLASMINOGEN ACTIVATOR INHIBITOR TYPE 1 (PAI-1) AND ENDOMETRIAL CANCER

Yrd. Doç. Dr. Malik Ejder Yıldırım
Cumhuriyet Uni/Med. Gen.
Yrd. Doç. Dr. Hande Küçük Kurtulgan
Cumhuriyet Uni/Med.Gen.
Dr. Serpil Ersan
Cumhuriyet Uni/Med. Biochemistry
Yrd. Doç. Dr. Savas Karakus
Cumhuriyet Uni/ Obst.&Gyneco.
Yrd. Doç. Dr. Hasan Kılıçgün
Erzincan Uni/ Nutri. & Diet.
Prof. Dr. Sevtap Bakır
Cumhuriyet Uni/Med. Biochemistry

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Objective

- Plasminogen activator inhibitor type 1 (PAI-1) is a serine protease inhibitor (Serpine 1) and it inhibits both tissue plasminogen activator and urokinase plasminogen activator which are important in fibrinolysis. We aimed to find whether there is a possible association between PAI-1 level, PAI-1 4G/5G polymorphism and endometrial cancer.

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- Plasminogen which is pivotal regulator in fibrinolysis can be converted into plasmin by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Plasmin is a serine protease involved in intravascular dissolution of fibrin clots (3). PAI-1 is an important factor in the regulation of endogenous fibrinolysis by inhibiting both t-PA and u-PA.

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- The PAI-1 gene is located on chromosome 7 (7q21.3-q22). There is a common polymorphism known as 4G/5G in the promoter region (Guanosine insertion/deletion gene polymorphism) of this gene. Homozygosity for the deletion allele (4G/ 4G) has been associated with higher PAI-1 concentrations than the insertion genotype (5G/5G), and reduced fibrinolytic activity

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- Endometrial cancer is the common disease of the endometrium and it is a major problem for women's health. The level of PAI-1 may be an important marker for the formation and the prognosis of endometrial cancer. Some researchers also declared that the PAI-1 4G/5G polymorphism may contribute to cancer susceptibility and the 4G allele of PAI-1 may be associated with an increased risk of endometrial cancer.

Materials and methods

- Our study was approved by the Ethics Committee in Cumhuriyet University, Sivas, Turkey. 82 patients who were diagnosed as endometrial cancer and 76 female healthy controls were included in this study. The exact diagnoses of the patients were performed histopathologically. The patients were also classified in terms of the tumor grades. Individuals who had alcohol story, obesity problem and smokers were excluded. The age and body mass index (BMI) of the patients and control group was recorded.

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- Cytosolic concentrations of PAI-1 were determined by enzyme-linked immunoassay (ELISA) using Human PAI-1 ELISA Kit on a Triturus Analyser (Diagnostics Grifols, Spain). The genomic DNA was extracted from the peripheral blood using DNA isolation kit. Relevant gene sequences were amplified in a single (multiplex) amplification reaction and they were screened for PAI-1 4G/5G polymorphism using reverse hybridization strip assay procedure.

	Patients	Controls	P
Age (years)	60.5 ± 7.5	59.9 ± 7.7	>0.05
	(40-87)	(35-72)	
BMI	22.2 ± 3.6	(21.4± 4.1)	>0.05
Grade			
Grade 1	56 (68.3%)		
Grade 2	16 (19.5%)		
Grade 3	10 (12.2%)		

Table I. The characteristics of the patients and controls

Groups	(n)	PAI-1 level (ng/ml)	P
Patients	82 (51.9%)	14.88 ± 2.52	P< 0.001
Controls	76 (48.1%)	12.08 ± 2.01	

Table II. PAI-1 levels of the patients and controls.

Grade	(n)	PAI-1 level (ng/ml)	P
Grade 1	56 (68.3%)	14.50 ± 2.40	P= 0.047
Grade 2-3	26 (31.7%)	15.69 ± 2.63	

Table III. PAI-1 levels of Grade 1 and Grade 2+3 endometrial cancer patients.

	Patients (n=82)	Controls (n=76)	P
Genotype			
5G/5G	9 (11%)	22 (28.9%)	
4G/5G	51 (62.2%)	43 (56.6%)	P= 0.008
4G/4G	22 (26.8%)	11 (14.5%)	
Allele			
5G	69 (42.1%)	87 (57.2%)	P=0.026
4G	95 (57.9%)	65 (42.8%)	

Odds ratio: 0.554 (0.33-0.93)

Table IV. The distribution of PAI-1 4G/5G polymorphism and 4G/5G allelic frequency in the patients and controls.

	Grade 1 (n=56)	Grade 2+3 (n=26)	P
Genotype			
5G/5G	6 (10.7%)	3 (11.5%)	
4G/5G	35 (62.5%)	16 (61.5%)	P= 0.993
4G/4G	15 (26.8%)	7 (27%)	
Allele			
5G	47 (42%)	22 (42.3%)	P= 0.967
4G	65 (58%)	30 (57.7%)	

Odds ratio: 0.986 (0.507-1919)

Table V. The distribution of PAI-1 4G/5G polymorphism and 4G/5G allelic frequency in the Grade 1 and Grade 2+3 endometrial cancer patients.

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Regular Article

Plasminogen activator inhibitor-1 (PAI-1) 4 G/5 G polymorphism and endometrial cancer. Influence of PAI-1 polymorphism on tissue PAI-1 antigen and mRNA expression and tumor severity

Juan Gilabert-Estellés [a,1], Luis A. Ramón [b,1], Aitana Braza-Boïls [b], Juan Gilabert [c], Melitina Chirivella [d], Francisco España [b], Amparo Estellés [b,*]

[a] Gynecology Service, Hospital Universitario Dr Peset, Valencia, Spain
[b] Research Center, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[c] Gynecology Service, Hospital Arnau de Vilanova, Valencia, Spain
[d] Anatomopathology Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain

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ABSTRACT

Plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism may have significance for PAI-1 expression. High levels of PAI-1 in endometrial cancer patients are associated with a poor prognosis. The objective of this study was to evaluate the PAI-1 4G/5G polymorphism in women with and without endometrial cancer and to analyze the influence of this polymorphism on PAI-1 expression in endometrial tissue.

In 423 women (212 patients with endometrial cancer and 211 controls) PAI-1 4G/5G polymorphism was determined by PCR amplification using allele-specific primers. Quantitative real-time RT-PCR assay was used to quantify PAI-1 mRNA and PAI-1 protein levels were quantified by ELISA in tissue extracts from 33 patients with endometrial cancer and from 70 endometrial tissues from control women. The frequency of PAI-1 4G/4G genotype ($P=0.010$) and the PAI-1 4G allele ($P=0.009$) was significantly higher in patients than in controls. The frequency of PAI-1 4G allele was significantly higher in patients with stage IB than in those with stage IA ($P=0.03$). Control women with the 4G/4G genotype had higher endometrial PAI-1 protein ($P=0.018$) and mRNA ($P=0.004$) levels than those with the 5G/5G genotype. A significant increase in PAI-1 protein and mRNA was observed in endometrial cancer tissue in comparison with the endometrial tissue from control women ($P<0.01$). In conclusion, frequencies of the PAI-1 4G allele and 4G/4G genotype were found significantly more often in women with endometrial cancer than in controls. PAI-1 levels in endometrial

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- The frequency of PAI-1 4G/4G genotype and the PAI-1 4G allele was significantly higher in endometrial cancer patients than in controls. The frequency of PAI-1 4G allele was significantly higher in patients with stage IB than in those with stage IA. The individuals with the 4G/4G genotype had higher endometrial PAI-1 protein. PAI-1 levels in endometrial tissue seem to be associated with PAI-1 4G/5G polymorphism.

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PAI-1 promoter 4G/5G polymorphism (rs1799768) contributes to tumor susceptibility: Evidence from meta-analysis

XIN XU, YANQI XIE, YIWEI LIN, XIANGLAI XU, YI ZHU, YEQING MAO, ZHENGHUI HU, JIAN WU, HONG CHEN, XIANGYI ZHENG, JIE QIN and LIPING XIE

Department of Urology, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, P.R. China

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Abstract. Plasminogen activator inhibitor-1 (PAI-1), belonging to the urokinase plasminogen activation (uPA) system, is involved in cancer development and progression. The PAI-1 promoter 4G/5G polymorphism was shown to contribute to genetic susceptibility to cancer, although the results were inconsistent. To assess this relationship more precisely, a meta-analysis was performed. The electronic databases PubMed, Scopus, Web of Science and Chinese National Knowledge Infrastructure (CNKI) were searched; data were extracted and analyzed independently by two reviewers. Ultimately, 21 eligible case-control studies with a total of 8,415 cancer cases and 9,208 controls were included. The overall odds ratio (OR) with its 95% confidence interval (CI) showed a statistically significant association between the PAI-1 promoter 4G/5G polymorphism and cancer risk (4G/4G

evidence has shown that plasminogen activator inhibitor-1 (PAI-1), belonging to the urokinase plasminogen activation (uPA) system, plays an important role in signal transduction, cell adherence and cell migration, thus promoting invasion and metastasis (2). In addition, PAI-1 concentrations and mRNA levels in primary tumor tissues correlate with adverse patient outcome in multiple cancer types (3-6). Recently, the first level-of-evidence-1 (LOE-1) cancer biomarker, PAI-1, entered clinical practice in breast cancer management (7).

The PAI-1 gene is located on chromosome 7 and contains 8 introns and 9 exons (8). Gene variability may contribute to the level of PAI-1 biosynthesis. Among the variants of the PAI-1 gene, the PAI-1 4G/5G polymorphism (rs1799768) has been the most frequently studied. The 4G allele of 4G/5G insertion/deletion polymorphism located in the promoter

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- PAI-1 4G/5G polymorphism most likely contributes to susceptibility to cancer, particularly in Caucasians. Furthermore, the 4G allele may be associated with an increased risk of endometrial cancer.

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Tumor-Associated Proteolytic Factors uPA and PAI-1 in Endometrial Carcinoma

U. Köhler[1], K. Hiller, R. Martin, D. Langanke, G. Naumann, K. Bilek, F. Jänicke, M. Schmitt
[1] To whom correspondence and reprint requests should be addressed at Universitäts-Frauenklinik, Philipp-Rosenthal-Str. 55, 04103 Leipzig, Germany.

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Abstract References

Abstract

The levels of plasminogen activator urokinase (uPA) and of its inhibitor (PAI-1) were measured by use of ELISA in the cytosol of tissue homogenates obtained from endometrial carcinomas and the marginal, tumor-free endometrium of postmenopausal patients (n= 64). Significantly higher median levels of uPA and PAI-1 were found in malignant endometrium (uPA 1.89 ng/mg, PAI-1 3.04 ng/mg) compared to tumor-free endometrium (uPA 0.84 ng/mg, PAI-1 1.01 ng/mg). Concerning uPA, no significant differences were found in dependence on histomorphological prognostic factors (staging, grading), but the median level of PAI-1 was significantly higher in G2/G3 carcinomas compared to G1 tumors (5.08 ng/mg vs 2.19 ng/mg). Because of the good prognosis of operated patients with endometrial carcinomas, the prognostic value of uPA and PAI-1 can only be decided by a larger number of patients and a long observation time.

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- Significantly higher median levels of PAI-1 were found in malignant endometrium (uPA 1.89 ng/mg, PAI-1 3.04 ng/mg) compared to tumor-free endometrium (uPA 0.84 ng/mg, PAI-1 1.01 ng/mg). The median level of PAI-1 was significantly higher in G2/G3 carcinomas compared to G1 tumors.

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QUARTERLY

Plasminogen activator inhibitor-1 (PAI-1) gene 4G/5G promoter polymorphism is not associated with breast cancer[o]

Janusz Błasiak[✉] and Beata Smolarz

Department of Molecular Genetics, University of Łódź, St. Banacha 12/16, 90-237 Łódź, Poland

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Key words: plasminogen activator inhibitor-1 (PAI-1), *PAI-1* gene, gene polymorphism, breast cancer, prognostic marker

The antigen content of plasminogen activator inhibitor-1 (PAI-1) in primary breast cancer tissue extracts may be of strong prognostic value: high levels of PAI-1 in tumors predict poor prognosis for patients. The gene encoding PAI-1 is highly polymorphic and an insertion (5G)/deletion (4G) polymorphism in the *PAI-1* gene promoter (the 4G/5G polymorphism), may have functional significance in *PAI-1* expression. In the present work the distribution of genotypes and frequency of alleles of the 4G/5G polymorphism in subjects with breast cancer were investigated. Tumor tissues were obtained from 100 postmenopausal women with node-negative and node-positive ductal breast carcinoma with uniform tumor size. Blood samples from age matched healthy women served as control. The 4G/5G polymorphism was determined by PCR amplification using the allele specific primers. The distribution of the genotypes of the 4G/5G polymorphism in both control and patients did not differ significantly ($P > 0.05$) from those predicted by the Hardy-Weinberg distribution. There were no differences in the genotype distributions and allele frequencies between node-positive and node-negative patients. The 4G/5G polymorphism may not be linked with elevated level of PAI-1 observed in breast cancer and therefore may not be associated with appearance and/or progression of breast cancer.

Cancer progression, leading to its invasion and eventually to metastasis, is a multifactorial process that includes adherence to the basement membrane, secretion of proteolytic enzymes and cancer cell migration into vessels and lymphatic nodes followed by extravasation at distant sites [1]. A critical step of the progression is crossing tissue boundaries by the malignant cells which distinguishes proliferative disorders and carci-

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[✉]Send all correspondence to Janusz Błasiak, fax (48 42) 635 4484; e-mail januszb@biol.uni.lodz.pl

Abbreviations: PAI-1, plasminogen activator inhibitor-1; ECM, extracellular matrix; uPA, urokinase type plasminogen activator; tPA, tissue type plasminogen activator; uPAR, urokinase receptor.

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- The 4G/5G polymorphism may not be linked with elevated level of PAI-1 observed in breast cancer and therefore may not be associated with appearance and/or progression of breast cancer. On the other hand, the distribution of the genotypes of the 4G/5G polymorphism between controls and patients was not different significantly.

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Comparative study on expression of plasminogen activator inhibitor 1 and its mRNA in endometrial cancers and normal endometria.

Fujimoto J[1], Hori M, Ichigo S, Hirose R, Sakaguchi H, Tamaya T.

Author information

Abstract

The effects of the endocrine milieu on growth, invasion and metastasis, associated with neovascularization of endometrial cancer, the expression of plasminogen activator inhibitor 1 (PAI-1), and its mRNA in endometrial atypical hyperplasia and cancer, and normal endometria as controls were determined in premenopausal and postmenopausal women. In premenopausal women, the levels of PAI-1 and its mRNA in normal endometria were significantly higher than in endometrial atypical hyperplasia and cancer. On the other hand, in postmenopausal women, the results were reversed. There was no difference in the expression of PAI-1 and its mRNA in the various histological grades and clinical stages in endometrial cancers, while the expression of PAI-1 in other cancers increased during tumor progression. In our previous study, the expression of PAI-1 and its mRNA in well-differentiated endometrial cancer cell lines was dependent upon estrogen and progesterone. This might be partially related to the endocrine milieu, especially in endometrial atypical hyperplasia and well-differentiated endometrial cancer, which seems to be dependent on sex steroids. Therefore, endometrial cancer of any histological grade and clinical stage might maintain PAI-1 expression in both premenopausal and postmenopausal women, which may modulate, at least in part, growth, invasion and metastasis associated with neovascularization of endometrial cancer.

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- In premenopausal women, the levels of PAI-1 and its mRNA in normal endometria were significantly higher than in endometrial atypical hyperplasia and cancer. On the other hand, in postmenopausal women, the results were reversed. There was no difference in the expression of PAI-1 and its mRNA in the various histological grades and clinical stages in endometrial cancers, while the expression of PAI-1 in other cancers increased during tumor progression.

International Journal of Oncology

Plasminogen activation system in oral cancer: Relevance in prognosis and therapy (Review)

Authors: Marzena Wyganowska-Świątkowska, Jerzy Jankun

View Affiliations

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Abstract

Research on carcinogenesis and progress in cancer treatment have reduced mortality of cancer patients. Mortality rates decreased by 1.5% per year from 2001 through 2010 for most types of cancer in men and women. However, oral cancer is still a significant global health problem since incidence and mortality rates are increasing. Oral cavity cancer is ranked the 8th in men and the 14th in women based on data collected between 2006 and 2010 by the National Institute of Health. Furthermore, an increasing incidence of head and neck neoplasms, particularly the tongue cancer among young adults has been reported recently. It is most likely due to increasing human papillomavirus (HPV) infection or the early start of tobacco and alcohol consumption. Treatment of oral cancer patients is mainly surgical and often leads to esthetic and functional deformities, with severe impact on the quality of life. Thus, novel form of treatments and selection of patients with high and low risk of mortality is of high priority for clinical studies. The expression of proteolytic enzymes in tumor and stromal tissues has been shown to have prognostic significance in many human cancers and

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- Overexpression of PAI-1 favors angiogenesis, metastasis and poor prognosis, although when applied in very high concentrations it inhibits angiogenesis and tumor growth, the phenomenon is described as the PAI-1 paradox. PAI-1 inhibits the activity of matrix metalloproteinases, which play a crucial role in invasion of malignant cells through the basal lamina and inhibiting proteolysis can reduce tumor growth in many in vivo and in vitro models.

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- Based on this study, it can be thought that the level of PAI-1 and PAI-1 4G/5G polymorphism are effective in the formation of endometrial cancer and PAI-1 level may be associated with the grade of this tumor.

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- If it consists of a common idea about the effect of PAI-1 levels and 4G/5G polymorphism on endometrial cancer, PAI-1 may be a therapeutic target for this cancer in the future.

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TEŞEKKÜRLER