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ORIGINAL ARTICLE

ICAM-1 (Lys469Glu) and *PECAM-1 (Leu125Val)* polymorphisms in diffuse astrocytomas

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Abstract Cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and platelet-endothelial cell adhesion molecule-1 (PECAM-1) play an important role in glioma invasion and angiogenesis. The aim of this study was to investigate whether specific genetic polymorphisms of *ICAM-1* and *PECAM-1* could be associated with glioma development and progression. Single-nucleotide polymorphism in codon 469 of *ICAM-1* and codon 125 of *PECAM-1* were examined in 158 patients with astrocytomas and 162 controls using polymerase chain reaction and restriction enzyme analysis. The distribution of *PECAM-1* polymorphic genotypes in astrocytomas did not show any significant difference. However, a specific *ICAM-1* genotype (*G/G*, corresponding to *Lys469Glu*) exhibited higher frequency in grade II astrocytomas compared to controls, grade III, and grade IV astrocytomas; suggesting that this polymorphism could be involved in the development of grade II astrocytomas.

Keywords Astrocytoma · Polymorphism · PECAM-1 · ICAM-1

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Introduction

Astrocytomas are the most common type of primary human brain neoplasms, accounting for more than 60% of them. They form a heterogeneous group of tumors and are classified into grades, ranging from I to IV. Grade I astrocytomas have relatively benign appearance with minimal atypia or anaplasia. Grades II–IV are classified as diffusely infiltrating astrocytomas, presenting increased degree of malignancy [1].

Grade II diffuse astrocytomas are slow-growing tumors; however, exhibits invasive features and spontaneous progression to higher grades [2, 3]. Anaplastic astrocytomas (grade III) can develop from low-grade astrocytomas (grade II), or be diagnosed at first biopsy without a precursor lesion, they have a greater degree of anaplasia than grade II [4, 5]. Glioblastomas (grade IV) are the most malignant and frequent astrocytic tumors. They originated from a diffuse or anaplastic astrocytoma (secondary glioblastoma) or it

may manifest "de novo" as a primary glioblastoma [6, 7]. This tumor is highly infiltrative and exhibits high mitotic activity, necrotic areas, and microvascular proliferation [2, 4, 8]. Genetic studies suggest that there are several pathways leading to malignant gliomas progression and they can be classified based on specific gene mutations and/or gross chromosomal aberrations, with differential expression of specifics genes and proteins [9].

The biological features of gliomas require disruption of endothelial cell–cell attachment and cell-matrix adhesion, cell migration, and formation of new cell–cell interactions [10] and there are increasing evidences for the importance of adhesion molecules in the complex process of tumor development, invasion, metastasis, and interaction with immune cells [11–15]. Cell adhesion molecules, including ICAM-1 and PECAM-1, participate of this process and contribute to the local infiltrative ability of gliomas behavior [16].

Intercellular adhesion molecule-1, a single-chain 76–110 kDa glycoprotein, is a member of the immunoglobulin superfamily [17]. Several studies have demonstrated that ICAM-1 is expressed in human glioma cells and this expression is affected by cytokines [18–20]. The expression of ICAM-1 in high-grade gliomas was previously reported, and the same study showed weakly expression in low-grade gliomas and no expression in normal brain [18]. In addition to that other study demonstrated that intratumoral endothelial cells either express ICAM-1, suggesting its relevance in attracting circulating lymphocytes to intratumoral sites [21].

Platelet-endothelial cell adhesion molecule-1 is a 130 kDa glycoprotein that belongs to the family type-I transmembrane cell adhesion molecules that are member of the immunoglobulin superfamily [22, 23]. This protein is an important participant in the adhesion cascade, leading the leucocytes migration during the inflammatory process [23]. It is involved in the chemokine-induced angiogenesis [24–26], and also modulates endothelial cell migration "in vitro" [27]. The expression of PECAM-1 was reported in tumor cells [28] and probably favors the angiogenesis process by promoting specific interactions between glial and endothelial cells [9].

Gene polymorphisms analysis of adhesion molecules have been well described and, in some cases, contribute to the understanding of genetic variability underlying the development of several diseases as acute myocardial infarction [28].

ICAM-1 gene, located on chromosome 19p-13, exhibits a common and functionally important genetic polymorphism [29]. Two biallelic polymorphisms in the coding sequence of *ICAM-1* were identified: Gly or Arg at codon 241 (exon 4), and Lys or Glu at codon 469 (exon 6) in Ig domain 5 [30]. The latter is an A–G substitution at position located three bases upstream of an mRNA splicing site that influence RNA splicing patterns. In fact, cells of the *GG* genotype produce less mRNA for the ICAM-1-S isoform than *AA* cells. Because ICAM-1-S has no transmembrane or intracellular domains, signal transduction by ICAM-1 is, therefore, affected [31]. Several studies have reported a correlation between these single-nucleotide polymorphisms (SNPs) and many inflammatory diseases, including Behcet's disease [32], type-1 diabetes [33], Graves' disease [34], multiple sclerosis [35] and rheumatoid arthritis [36].

Platelet-endothelial cell adhesion molecule-1 polymorphisms were described in functionally important domains [37, 38]. These polymorphisms are located in exon 3 at codon 80 changing a valine to methionine (*Val80Met*), at codon 125 changing a leucine to valine (*L125 V*), in exon 8 at codon 563 changing an asparagine to serine (*N563S*), and in exon 12 at codon 670 changing a glycine to arginine (*G670R*) [39]. *Val125* and *Asn563* were correlated to increased risk of atherosclerosis [40, 41] and multiple sclerosis [42]. Owing to its strategic role in the cell–cell interaction, genetic variation in *PECAM-1* may have a prime biological effect in inflammatory or organ-specific autoimmune processes, which require migration of pathogenetic cells into target organs [43].

The possible role of polymorphisms of cell adhesion molecules in the development of gliomas has not yet been investigated. Taken into account the relevance of cell adhesion molecules in microvascular proliferation and tumor invasion, hallmarks of malignant gliomas, the aim of this study was to investigate *ICAM-1* codon 469 and *PECAM-1* codon 125 SNPs in diffusely infiltrating astrocytomas.

Materials and methods

Patients and controls

This study involved 320 unrelated individuals divided into 158 patients with astrocytomas and 162 controls (mean age 48.4 years), with similar ethnic characteristics. Gender distribution was 97 males/61 females, and 97 males/65 females, for patients and controls, respectively. These groups were composed of individuals recruited from 2002 to 2005 in the Clinical Hospital of Ribeirão Preto School of Medicine of University of São Paulo (HC-FMRPUSP), Clinical Hospital of School of Medicine of University of São Paulo (HC-FMUSP), and São Paulo Hospital of Federal University of São Paulo (UNIFESP); Brazil.

The distribution of 158 patients in astrocytomas subtypes was: 26 grade II, 26 grade III and 106 grade IV. On the basis of phenotype characteristics and family history, 120 patients and 113 controls were identified as white

(European descendents); 27 patients and 27 controls mulatto, 8 and 13 black (African descendents); 2 and 8 were oriental descendents; 1 and 1 were classified as others. Epidemiological data from the study population were obtained by a standard interviewer-administered questionnaire, including data on social habits, health problems and ancestry. The human subject protocol was approved by local Ethics Committee of the participating institutions and written informed consent was obtained from all subjects or their parents.

Genotyping

DNA extraction

Blood was collected in EDTA-containing tubes and genomic DNA was extracted from peripheral blood lymphocytes by the conventional phenol–chloroform method. Isolated DNA was re-suspended in Tris–EDTA buffer (pH 8.0) and was stored at −20°C until use.

ICAM-1 polymorphism

The genotyping assay for the *ICAM-1* codon 469 polymorphism was performed by polymerase chain reaction (PCR) approach described by Nejentsev et al. [33] with modifications. The PCR primers used were as follows: forward primer 5′-GGAACCCATTGCCCGAGC-3′; reverse primer 5′-GGTGAGGATTGCATTAGGTC-3′. The PCR was performed in a total volume of 25 μl containing 150 ng of genomic DNA, 100 ng of each primer, 200 μM dNTPs, 2.5 μl of 10× PCR buffer (1×: 200 mM Tris–HCl, 500 mM KCl, pH 8.4), 1.5 mM $MgCl_2$ and 1.25 U *Taq* DNA polymerase (Invitrogen, Carlsbad, CA, USA). The cycling conditions consisted of: 1 cycle of 1 min at 96°C, followed by 30 cycles of 20 s at 96°C, primer annealing at 64°C for 50 s and polymerization at 72°C for 1 min; and a final extension at 72°C for 5 min. Amplified PCR products were subsequently digested for 3 h at 60°C using three units of the restriction enzyme BstUI (New England BioLabs, Beverly, MA, USA) in a final volume of 25 μl. Restriction-fragment length polymorphism was then detected using electrophoresis on an ethidium bromide-stained 2.0% agarose gel (Sigma-Aldrich, St Louis, MO, USA). In the presence of the *G* allele (*Glu469*), a *BstUi* restriction site was present, thus resulting in fragments of 136 and 87 bp, while in the presence of the allele A (*Lys469*) only the uncut 223 bp PCR product was observed.

PECAM-1 polymorphism

Genotypic analysis of the *PECAM-1* codon 125 gene polymorphism was determined using a modification of a PCR–RFLP (restriction-fragment length polymorphism) approach described previously by Nichols et al. [44]. The PCR primers used were as follows: forward primer 5′-ACGGTGCAAAATGGGAAGAA-3′; reverse primer 5′-AGAGGGTGATGGGTGGAGAG-3′. A DNA fragment of 364 bp was amplified using the same PCR mixture indicated above. Initial denaturation was carried out at 94°C for 5 min, followed by 35 cycles at 94°C for 30 s, 62°C for 40 s and 72°C for 1 min. A final extension step of 72°C for 5 min terminated the process. After amplification, 20 μl of the PCR product was digested with five units of the restriction enzyme *Alu*I (New England BioLabs, Beverly, MA) in a final volume of 25 μl. In the presence of the *C* allele (*Leu125*), two fragments of 315 and 49 bp were observed; while the *G* allele (*Val 125*) resulted in fragments of 237, 78 and 49 bp.

Statistical analysis

Statistical analysis was performed using GraphPad InStat software (GraphPad Software Inc., CA, USA). The groups were submitted to a statistical analysis with χ^2 test or Fisher′s exact test. Differences were considered significant at $P < 0.05$. The 95% confidence intervals (95% CI) of the percentage were calculated by assuming a binomial distribution. Sex-age-adjusted odds ratio (ORs) and 95% CI were calculated according to an unconditional logistic model.

Results

Polymerase chain reaction and RFLP results confirmed the presence of the SNPs *ICAM-1 Lys469Glu* and *PECAM-1 Leu125Val* in the study subjects. Genotype and allelic frequencies for both SNPs were compared between astrocytoma patients and controls, and within astrocytomas subgroups (Table 1).

When all astrocytomas were pooled, their distribution of genotypes *AA*, *AG* and *GG* for *ICAM-1* codon 469 was not significantly different from controls ($P = 0.36$, 0.99, and 0.44, respectively). However, when the astrocytomas were discriminated by grade, we observed that the genotype *GG* was significantly higher in grade II astrocytomas compared to controls ($P = 0.03$; OR = 0.21; 95% CI = 0.06–0.77) and to higher grade astrocytomas [grade III astrocytoma ($P = 0.03$; OR = 0.05; 95% CI = 0.002–1.02) and grade IV astrocytoma ($P = 0.03$; OR = 0.18; 95% CI = 0.04–0.75)]. In general, we observed a significantly higher frequency of the allele *G* in grade II astrocytomas when compared to grade III ($P = 0.04$) and IV astrocytomas ($P = 0.02$) but not to controls ($P = 0.09$).

On the other hand, genotyping of *PECAM-1* detected the *Leu125Val* SNP, but the distribution frequency of the

Table 1 Genotypes (number and (%) of individuals) and allele frequencies of *ICAM-1 Lys469Glu* and *PECAM-1 Leu125Val* for controls and astrocytomas patients

Polymorphism	All astrocytomas	Grade II astrocytomas	Grade III astrocytomas	Grade IV astrocytomas	Controls
ICAM-1(Lys469Glu)					
A/A	75/158 (47.5)	8/26 (30.8)	15/26 (57.7)	52/106 (49.1)	69/162 (42.6)
A/G	72/158 (45.6)	13/26 (50.0)	11/26 (42.3)	48/106 (45.3)	84/162 (51.6)
G/G	11/158 (6.9)	5/26 (19.2)[a]	0/26 (0)	6/106 (5.7)	9/162 (5.6)
A/G + G/G	83/158 (52.5)	18/26 (69.2)	11/26 (42.3)	54/106 (50.9)	93/162 (57.4)
Allele frequency					
A	0.74	0.56	0.79	0.72	0.69
G	0.26	0.44	0.21	0.28	0.31
PECAM (Leu125Val)					
C/C	34/158 (21.5)	5/26 (19.2)	6/26 (23.1)	23/106 (21.7)	43/162 (26.5)
C/G	82/158 (51.8)	13/26 (50.0)	11/26 (42.3)	58/106 (54.7)	77/162 (47.5)
G/G	42/158 (26.5)	8/26 (30.8)	9/26 (34.6)	25/106 (23.5)	42/162 (25.9)
C/G + G/G	124/158 (78.5)	21/26 (80.8)	20/26 (76.9)	83/106 (78.3)	119/162 (77.5)
Allele frequency					
C	0.47	0.44[b]	0.44	0.49	0.43
G	0.53	0.56	0.56	0.51	0.57

A/A and *C/C* homozygous for the wild-type allele, *A/G* and *C/G* heterozygous, *G/G* (*ICAM-1 469Glu*) and *G/G PECAM-1125Val*) homozygous for the polymorphism allele

[a] The homozygous ICAM-1 *G/G* variant was significantly more prevalent in the grade II astrocytomas patients than in grade III and grade IV astrocytomas, and control subjects ($P = 0.03$)

[b] Allelic frequency in grade II astrocytomas patients is significantly higher than in grade III and IV astrocytomas ($P = 0.04$ and 0.02, respectively)

alleles CC, CG, and GG was not significantly different between controls and astrocytomas, either pooled or discriminated by grade.

For *ICAM-1 G/G* the median follow up times ranged between 0 and 266 weeks and the median survival time for *AA* group was 63 weeks, *AG* group was 54 weeks and *GG* group was 48 weeks; and for *PECAM-1 G/G* the median survival time for *AA* was 74 weeks, *AG* group was 52 weeks and for *GG* group was 57 weeks, and all these results were not significantly different among genotypes.

Brazilian population, as our control data, expressed *ICAM-1 Lys469Glu* and *PECAM-1 Leu125Val* polymorphism frequencies in agreement with those reported for other different populations (Japanese, Italian, Chinese, Asian, and Caucasian) as shown in Table 2. Multivariate analysis, including age, race, and gender as co-variables found no statistical difference between them.

Discussion

This is the first study to investigate the role of polymorphisms within the *ICAM-1* and *PECAM-1* genes in the susceptibility and development of diffuse astrocytomas. Two SNPs were selected for inclusion in the study, both encoding amino acid substitutions. These two polymorphisms (*ICAM-1 Lys469Glu* and *PECAM-1 Leu125Val*) influence the metabolism and stability of these adhesion molecules, including mRNA splicing and production of ICAM-1S [45, 46].

In the control group, we found that *ICAM-1* and *PECAM-1* alleles and genotypes were distributed consistently with the results reported in previous studies with Caucasian population that evaluated the *ICAM-1 Lys/Glu* and *PECAM-1 Leu/Val* gene polymorphisms [47, 48]. In contrast, the comparison between the frequencies of these polymorphisms obtained in our study with population predominantly Caucasian and other populations confirmed that the frequencies suffer modifications among populations (Table 2). These variations suggest that susceptibility genes may have different effects in ethnically distinct populations and that these effects depend on the allele frequencies [48].

Intercellular adhesion molecule-1 is aberrantly expressed in some central nervous system diseases, such as multiple sclerosis, and Alzheimer's disease [49–51]. Studies of ICAM-1 have suggested the association of the polymorphism *(Lys469Glu)* with several inflammatory diseases and they attribute it to the predominance of the *G* allele, while *A/A* homozygotes have been associated with multiple sclerosis [31]. In addition, ICAM-1 has been found to induce expression of several other proinflammatory cytokines, such

Table 2 Comparison of the *ICAM-1 Lys469Glu* and *PECAM-1 Leu125Val* and genotypes of the control subjects in this study and previously published studies

Genotype (%)			Allele (%)		Population	Study
A/A	A/G	G/G	A	G		
ICAM-1						
69 (42.6)	84 (51.6)	9 (5.6)	222 (68.5)	102 (31.5)	Brazilian	Our control data
Lys469Glu						
65 (38.9)	74 (44.3)	28 (16.8)	204 (61.1)	130 (38.9)	Japanese	[53]
22 (40.7)	25 (46.3)	7 (12.9)	68 (63.0)	40 (37.0)	Italian	[54]
36 (29.0)	70 (61.0)	10 (9.0)	139 (60.0)	93 (40.0)	German	[55]
118 (47.6)	107 (43.1)	23 (9.3)	342 (69.0)	154 (31.0)	Korean	[56]
28 (23.9)	67 (57.3)	22 (18.8)	123 (52.6)	111 (47.4)	Spanish	[57]
Genotype (%)			Allele (%)		Population	Study
C/C	C/G	G/G	C	G		
PECAM-1						
43 (26.5)	77 (47.5)	42(25.9)	163 (50.3)	161 (49.7)	Brazilian	Our control data
Leu125Val						
45 (19.2)	120 (51.1)	70 (29.8)	210 (44.7)	260 (55.3)	Japanese	[58]
38 (32.2)	49 (41.5)	31 (26.3)	125 (53.0)	111 (47.0)	Italian	[28]
35 (23.3)	86 (57.3)	29 (19.3)	156 (52.0)	144 (48.0)	Chinese	[45]
47 (42.7)	52 (47.3)	11 (10.0)	146 (66.4)	74 (33.6)	Asian	[59]
49 (28.8)	74 (43.5)	47 (27.7)	172 (50.6)	168 (49.4)	Caucasian	[48]

as interleukins IL-1 alpha, IL-1 beta, IL-6, and necrosis tumor factor (TNF) alpha, specifically in astrocytes [52]. Here, we compared the specific *A/G* polymorphism at codon 469 of *ICAM-1* in normal individuals versus astrocytomas patients, and found a higher frequency of the genotype *G/G* in grade II astrocytomas compared with controls and other astrocytomas grades. These data suggest a possible role for this polymorphism in the development of low-grade astrocytomas and raise an interesting question regarding their role in gliomas progression.

The presence of the polymorphism in grade II and not in grades III and IV gliomas can be explained by two hypothesis: grade II tumors presenting the polymorphism could have lower tendency to evolve to high grades, explaining the reason that this polymorphism was not detected in high-grade gliomas; or the hypothesis that the percentage of primary glioblastoma is so high, 95% according to the literature [1], that could difficult the identification of genetic abnormalities in secondary glioblastomas because the minimal number of cases. In the present study, none glioblastoma was considered secondary based on the absence of clinical history of progression from a low-grade tumor. To test these hypotheses above, a long and larger study should be necessary, where grade II astrocytoma patients could be followed for 5–10 years, until their disease progression and the number of secondary glioblastomas could be significant.

Several reports have suggested that PECAM-1 may have a role in glioma genesis. Higher level of soluble PECAM-1 isoform was observed in subjects homozygous for the *Val125* allele, suggesting that polymorphism in this allele could impact on its protein metabolism and stability [45]. Here, we analyzed the SNP *Leu125Val* in *PECAM-1*, but found no association of this polymorphism with the development or malignant progression of astrocytomas, suggesting that this specific heterogeneity of *PECAM-1* is not related with the biological behavior of these brain tumors.

Currently, different biological pathways are known to be associated with the progression of low-grade astrocytomas to anaplastic astrocytomas and glioblastomas, such as vascular density, nuclear atypia, mitosis, deletion of the *p16* gene, loss of heterozygosity on chromosomes 10 and 19q, inactivation of the retinoblastoma (*RB)* gene and *CDK4* amplification [6]. However, there is a lack of definitive markers to preview the evolution of grade II astrocytomas. Further genetic polymorphism studies with adhesion molecules could help to elucidate the mechanisms involved in gliomas progression and identify new prognostic markers to malignancy in diffuse astrocytomas.

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Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this manuscript.

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