Artigo / Article

Genetic polymorphisms of glutathione S-transferase mu1 and theta1 in patients with acquired aplastic anemia: A Brazilian experience

Polimorfismo genético da glutationa S -transferase mu1 e theta 1 em pacientes com anemia aplástica adquirida: uma experiência brasileira

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*The causes of acquired aplastic anemia (AAA) include immunologic mechanisms and oxidative DNA damage. Glutathione S-Transferase (GST) plays an important role in detoxification. In humans, GST genes encode four main clones: alpha (A), mu (M), pi (P) and theta (T). Among GST genes, GST M1 and T1 have null genotypes that result in a lack of activity. The aim of this study was to investigate polymorphisms of the GSTM1 and GSTT1 enzyme in Brazilian patients with AAA. The null allele of GSTM1 was observed in 3 (16.6%) patients and the GSTT1 null genotype was observed in only one (5.5%) patient. This study did not find any association between genetic polymorphisms of the GSTM1/GSTT1 detoxifying enzymes and the pathogenesis of AAA. Rev. bras. hematol. hemoter. 2007;**29**(4):344-345.*

Key Words: *Acquired aplastic anemia; gluthatione; genetic polymorphisms.*

Introduction

There are multiple causes for acquired aplastic anemia (AAA). Immunologic mechanisms and oxidative DNA damage have been implicated in the pathogenesis of AAA. Bone marrow protection from drugs and xenobiotics depends on an intact detoxification pathway.[1,2]

Glutathione S-Transferase (GST) is a family of enzymes that play an important role in detoxification by catalyzing the conjugation of many hydrophobic and electrophilic compounds with reduced glutathione. In humans, GST genes encode four main clones: alpha (A), mu (M), pi (P) and theta (T). Among the GST genes, GST M1 and T1 have null genotype that result in lack of enzyme activity.[3]

The ethnic origin of the Brazilian population is highly heterogeneous and is composed of immigrants from Europe, Asia and Africa and the indigenous population. The aim of this study was to investigate polymorphisms of the enzymes GSTM1 and GSTT1 enzymes in Brazilian patients with AAA.

Patients and Methods

Eighteen patients (9 man, 9 women; median age 42.5; range from 17 to 73 years) with diagnosis of AAA according to international criteria were studied.[4] Of these, nine were African-Brazilians and nine were Caucasian descendents. These patients attended the Acquired Anemia Out Patients Clinic of the Hematology and Blood Transfusion Service of Unifesp. All patients agreed to in participate and this study was approval by the Ethics Committee of Unifesp.

Genomic DNA was obtained from peripheral blood samples and the GSTM1 and GSTT1 genes were amplified by multiplex polymerase chain reaction as previously described.[5]

Results

Fourteen patients (77.7%) had GSTM1 +/ GSTT1 + genotypes; 3 (16.6%) were GSTM1 -/ GSTT1 + and one (5.5%) was GSTM1 +/ GSTT1 -. The combined null genotype of both genes (GSTM1 and GSTT1) was not observed.

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Table 1. Distribution of GSTM1 and GSTT1 polymorphisms in Caucasian and African-Brazilian patients with acquired aplastic anemia divided into responders and non-responders.

GST polymorphism	Caucasians N (%)	African-Brazilian N (%)	Responders N (%)	Non-responders N (%)
GSTM1+/GSTT1+	8 (57.1)	6 (42.9)	11 (78.6)	3 (21.4)
GSTM1-/GSTT1+	1(33.3)	2 (66.7)	1 (33.3)	2 (66.7)
GSTM1+/GSTT1-	- -	1 (100)	1 (100)	
	p = 0,5765		p = 0,5327	
	(considering GSTM1+/GSTT1+ vs GSTM1-/GSTT1+ or GSTM1+/GSTT1-)			

The null allele of GSTM1 was observed in 3 (16.6%) patients (two African-Brazilians and one Caucasian descendent); the GSTT1 null genotype was observed in only one (5.5%) patient (African-Brazilian).

Table 1 summarizes the response to treatment and GST genotypes for each AAA patient studied.

Discussion

The low prevalence for the null genotypes observed in both groups does not permit identifications of associations with the response to immunosuppressive therapy.

Our frequencies of GST null genotypes do not agree with previous findings in the Brazilian population which describe a high prevalence of the null allele of GSTM1 (55% and 33%) and GSTT1 (18.5% and 19%) among Caucasian descendents and African-Brazilians respectively.[5] However, the fact that the first studied the genotypes of healty individuals and the present study evaluated patients with AAA which may explain this discrepancy.

There was no significant genetic variation between Caucasian descendents and African-Brazilians, a fact that may be associated with immigration to this country.

Despite of the lower number of patients, the low frequency of null GST M1 or T1 in our study was in agreement with Dufour *et al*,[6] who suggested that genetic polymorphisms of the GSTM1 and GSTT1 detoxifying enzymes are not associated with the pathogenesis of AAA.

Lack of statistical significance in our results could be explained by low number of patients analyzed, and therefore further studies should be performed to evaluate risk factors for AAA among distinct ethnic groups in Brazil.

Resumo

*As causas de anemia aplástica adquirida (AAA) incluem mecanismos imunológicos e oxidativos de lesão ao DNA. Glutathiona S-transferase (GST) é fundamental na detoxicação celular. Em humanos, os genes da GST são codificados por quatro clones: alpha (A), mu (M), pi (P) e theta (T). Entre os genes da GST, GST M1 e T1 possuem um genótipo nulo que resulta em ausência de atividade enzimática. O objetivo deste estudo foi investigar os polimorfismos das enzimas GSTM1 e GSTT1 em pacientes brasileiros portadores de AAA. O alelo nulo da GSTM1 foi observado em três (16.6%) pacientes e o GSTT1 nulo foi observado somente em um (5.5%) paciente. Este estudo não encontrou associação entre os polimorfismos genéticos das enzimas de detoxicação GSTM1/ GSTT1 e a patogênese da AAA. Rev. bras. hematol. hemoter. 2007;**29**(4):344-345.*

Palavras-chave: *Anemia aplástica; glutationa; polimorfismos gênicos.*

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