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Relationship between Glutathione S Transferase P1 and Toll like Receptor 2 Polymorphisms and Infections in Sickle Cell Anemia

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Abstract

Infections are the most common complications in individuals with sickle cell anemia. The splenomegaly of these individuals results from erythrocytes being sequestrated, resulting in organ atrophy and fibrosis. However, even before splenomegaly, phagocytic capacity and antibody production are affected as a result of splenic activity, leading to functional asplenia and increased susceptibility to infections. The reactive oxygen species (ROS) produced by phagocytes when activated by pathogenic microorganisms act as bactericides. On the other hand, oxidative damage to erythroid cells also plays a crucial role in hemolysis. We investigated the influence of GSTP1 and TLR2 genetic polymorphisms on susceptibility to infections in 278 patients with sickle cell anemia. These proteins offer protection against oxidative damage and play a key role in host defense against infection, respectively. However, our results do not support any major role of GSTP1 or TLR2 polymorphisms in susceptibility to infection in subjects with sickle cell anemia.

Keywords: *SCA; TLR2; GSTP1;* inflammation*; oxidative stress.*

Abbreviations: GST, glutathione S transferase; ROS, reactive oxygen species; TLR2, Toll like receptor 2; SCD, sickle cell disease; HbS, hemoglobin S; HPLC, high performance liquid chromatography; PCR, polymerase chain reaction; RFLP-PCR, restriction fragment length polymorphism - polymerase chain reaction; SNPs, Single nucleotide polymorphisms; Del, deletion; Ins, insertion.

Introduction

Clinical manifestations of sickle cell anemia (SCA) vary widely, and the reasons for this heterogeneity are not fully understood [1]. Individuals with SCA typically suffer from functional hyposplenism. In young children with hyposplenism, infection is a major cause of illness and death [2]. According to a Brazilian study of sickle cell anemia deaths, infection, mostly sepsis, is the most common cause of death [3].

An example of molecules that play a key role in host defense against infectious and inflammatory processes are the Toll-like receptors (TLRs). TLRs are critical in the detection and recognition of microbial pathogens, as well as the generation of signals for producing proteins and pro-inflammatory cytokines [4]. The cytokines released in response to TLR activation, such as interleukins, promote the recruitment of macrophages and other leukocytes to the site of infection. A TLR2 polymorphism may result in decreased macrophage response to bacterial peptides, which results in a diminished

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immune response [5]. Attracted to sites of inflammation, neutrophils, basophils, and monocytes produce cytotoxic proteins such as proteases, collagenases, and elastases as well as reactive oxygen radicals, which cause oxidative stress. In turn, this damage promotes the activation of endothelium and the adhesion of cells [6].

In β-hemoglobinopathies (SCA and thalassemia), oxidative damage to erythroid cells plays a crucial role in hemolysis due to ineffective erythropoiesis in the bone marrow and short survival of red blood cells in circulation [7]. Smith et al reported that patients with SCA who had low levels of antioxidants in the plasma had more vaso-occlusive crises [8]. The occurrence of motivated vaso-occlusive crises may be triggered by several switches, including the interaction between sickled red blood cells and the endothelium, nitric oxide-induced spasm, and acute phase inflammation [9].

Multiple antioxidant enzymes are present in cellular organelles, including glutathione S-transferases (GSTs), which provide protection from oxidative and chemical stress. [10]. Soluble GST family subunits are placed in various mutagenic classes, including Alpha, Mu, Pi, and Theta. However, GSTP1 appears to be the most widely distributed isoenzyme [11, 12]. Since many GST genes are polymorphic, there has been considerable interest in determining the particular allelic variants and those associated with increased risk of various diseases [13, 14]. The aim of this study was to investigate whether *GSTP1* and *TLR2* polymorphisms influence susceptibility to infection in sickle cell patients. It is possible that genotypes that lead to an inefficiency of metabolic pathways involved in antioxidant mechanisms or pathogen recognition increase the chances of infectious processes in SCA.

Methodology

Casuistry

A case-control study was conducted with samples of 278 patients using the following inclusion criteria: being with sickle cell anemia (Hb SS) unrelated, over the age of 18, and followed at the Foundation of Hematology and Hemotherapy of Pernambuco (HEMOPE). Cases: 207 with infection, and controls: 60 without infections.

Ethical Aspects of Research

This study was performed after approval by the Research Ethics Committee of HEMOPE under No. 016/2011 and developed fully complying with the ethical principles set out in Resolution 196/96 of the National Health Foundation.

Hematologic and Clinical Analysis

Analysis of hematological data was performed using an electronic cell counter (STKS, Coulter Corporation, FL, USA). The quantification of fetal hemoglobin and S was performed by high-performance liquid chromatography (HPLC - VARIANT / Bio-Rad, CA, USA), and clinical data were obtained by the analysis of medical records of patients.

Molecular Analysis

DNA extracted by phenol-chloroform technique was amplified by RFLP-PCR (restriction fragment length polymorphism - polymerase chain reaction) using forward and reverse primers for GSTP1 polymorphism analysis (F: 5'-CCA GCT GTA GTT AGG TCA AG-3' and R: 5'-AGC AGG CAC CTG GGT AAG-3') [15]. The final volume of the reaction was 12,5 µL. The parameters used were: initial denaturation at 94°C for 5 minutes, followed by 30 cycles of denaturation at 94°C for 1 minute, annealing at 59°C for 90 seconds, extension at 72°C for 90 seconds, and a final extension at 72°C for 7 minutes. The PCR products were treated with *Alw*261 restriction enzyme for 5 minutes at 37°C. After this, the samples were subjected to electrophoresis on agarose gel 1% stained with ethidium bromide. Bands of 113 and 329bp were visualized corresponding to wild-type genotype (Ile/Ile), bands of 216pb and the thick band corresponding to bands 107 and 113pb regarding homozygous variant genotype (Val/Val), and all bands were visualized in the heterozygous variant genotype (Ile/Val). The bands of 107 and 113pb were observed on a polyacrylamide gel 10% stained with ethidium bromide, where eight samples were applied (one wild-type genotype, three heterozygous variants Ile/Val and four homozygous variants Val /Val).

In the analysis of TLR-2 polymorphism (-196 to -174 del) were used the primes forward 5'-CACGGAGGCAGCGAGAAA-3' and reverse 5'-CTGGGCCGTGCAAAGAAG-3' [16]. The PCR conditions were as follows: initial denaturation at 95°C for 5 minutes followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 60°C for 40 seconds, extension at 72°C for 40 seconds, and final extension at 72°C for 7 minutes. The products were analyzed by electrophoresis on 1.5% agarose gel. The band of 286 bp corresponded to the Ins/Ins genotype, the band of 264 bp corresponded to genotype Del/Del and the bands of 286 bp and 264 bp simultaneously matched the Ins/Del genotype. All the bands were then photographed on a UV transilluminator.

Statistical Analysis

The Odds ratio was calculated using GraphPad Prism 6.0 software with a 95% confidence interval. Thus, the association between the variant genotypes (homozygous and heterozygous) with infections in sickle cell anemia was evaluated.

Results and Discussion

GSTP1 polymorphism analysis

The average age of the patients was 35.6 ± 10.4 years.

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The distribution of frequency examined showed a higher percentage for the heterozygous variant genotype (Ile/Val) at 46.02%, followed by the wild genotype (Ile/Ile) at 36.23% and the lowest frequency of 17.75% for the homozygous variant (Val/Val). Such findings were similar to those found in two studies also conducted with the Brazilian population by Hatagima et al. [17] and Honma et al [18]. Kiss et al [19] and Ates et al [20] also obtained similar frequencies in studies carried out in Hungary and Turkey, respectively.

We did not find a statistically significant association between the variant genotypes (Ile / Val and Val / Val) and the risk of infection in patients with sickle cell anemia (Table 1). Silva et al found higher levels of glutathione and greater antioxidant capacity in patients with SCA who presented the Val / Val genotype. This was compared to those with the Ile / Ile genotype [21].

In the literature, it has been extensively studied the relationship between *GSTP1* Val genotypes and a variety of diseases. This includes determining the susceptibility to cancer, and responses to metabolism, efficacy, and toxicity of certain drugs [15, 19, 20, 22, 23]. The association not found in this study can be explained by the possibility that these individuals present antioxidant mechanisms to compensate for the deficiency in the activity of isoform GSTP1. It is imperative to note that GST enzymes are part of an integrated defense system, and the combined action of other enzymes such as γ-glutamylcysteine synthase (γGluCysS) and glutathione synthase guarantees the efficiency of this system. It provides glutathione, as well as carriers to facilitate the removal of GSH conjugates [24].

TLR2 polymorphism analysis

SNPs (Single nucleotide polymorphisms) in TLR2 have been associated with susceptibility to various infectious and inflammatory diseases such as leprosy [25], increased gram-negative sepsis risk [26], recurrent bacterial infections in children [27] and colorectal and cervical cancer [28, 29]. Also, a study linked variants in the non-coding region of the TLR2 gene with infections in pediatric sickle cell anemia [30].

The polymorphism corresponding to a deletion of 22 base pairs at position -196 to -174 of the TLR2 promoter region has been reported to alter the promoter activity, decreasing responsive promoters [31]. In this study, the wild homozygous genotype (Ins / Ins) was the most frequent in this population (58.27%), followed by the heterozygous variant genotype (Ins / Del, 40.65%) and finally the homozygous variant (Del / Del, 1.8%). The frequency of TLR2 polymorphism alleles investigated correlates well with previously published data on Brazilian, Japanese and German populations [32, 33, 34].

Individuals with the homozygous genotype for the deletion (Del / Del) showed a 95% increased chance of developing an infection compared to wild homozygotes (OR=1.95; CI=0.1 to 38.65) (Table 2). However, despite the central role of TLR2 in the recognition of pathogens and initiation of defense, this result was not statistically significant.

When pairing the analysis of polymorphisms of both genes (*GSTP1* Ile / Val and *TLR2* Ins / Del) for the development of infectious complications, we also did not find a statistically significant (OR=1.27, P= 0.61) (Table 3).

Woehrle et al. 2008 [35], studying 325 patients with septic shock, observed that in patients with sepsis caused by gram-positive bacteria, the variant profile TLR2 did not alter the pattern of cytokines produced, so, had no involvement in the immune response. TAHARA et al. 2008 [36] in Japan also studied polymorphisms -196 to -174 of the TLR2 gene, relating them to the risk of gastroduodenal disease induced by

Table 1: Association between GSTP1 variant genotype and the risk of infections in 278 patients with sickle cell disease

GSTP1 Genotype	*With infection*	*Without infection*	*Chi-square*	*Odds Ratio*	*CI* of 95%*	*P value*
Ile/Val	98	29	0.14	1.13	(0.60 - 2.08)	0.7
Val/Val	34	15	0.52	0.75	(0.35 - 1.16)	0.47
Ile/Val or Val/Val	132	44	0.01	1	(O.57 – 1.76)	1
Ile/Ile	75	25		1(reference)		

* ***Confidence interval***

Table 2: Association between TLR2 variant genotype and the risk of infection in 278 patients with sickle cell disease

Variant Genotype TLR2	*With infection*	*Without infection*	*Chi-square*	*Odds Ratio*	*CI*of 95%*	*P value*
Ins/Del	78	35	3.08	0.61	(0.35 – 1.06)	0.08
Del/Del	3	0	0.04	1.95	(0.1 – 38.65)	0.85
Ins/Del or Del/Del	81	35	2.63	0.63	(0.37 – 1.1)	0.1
Ins/Ins	127	35		1(reference)		

* ***Confidence interval***

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Table 3: Association between GSTP1 and TLR2 variant genotypes and the risk of infections in 278 patients with sickle cell disease

GSTP1 and TLR2 Genotypes	With infection	Without infection	Chi-square	Odds Ratio	CI* of 95%	P value
GSTP1(Ile / Val) and TLR2(Ins / Del)	43	17	0.95	0.67	(0.3 – 1.5)	0.33
GSTP1(Ile / Ile) and TLR2(Ins / Ins)	53	14		1(reference)		
GSTP1(Ile / Val) and TLR2(Ins / Del)	43	17	0.25	1.27	(0.5 – 3.16)	0.61
GSTP1(Ile / Ile) and TLR2(Ins / Ins)	22	11		1(reference)		
GSTP1(Ile / Val) and TLR2(Ins / Del)	43	17	1.71	0.57	(0.25 – 1.3)	0.19
GSTP1(Ile / Val) and TLR2(Ins / Ins)	53	12		1(reference)		
GSTP1(Val / Val) and TLR2(Ins / Del)	14	6	0.72	0.62	(0.2 – 1.89)	0.39
GSTP1(Ile / Ile) and TLR2(Ins / Ins)	53	14		1(reference)		
GSTP1(Val / Val) and TLR2(Ins / Del)	14	6	0.01	1.05	(0.3 – 3.6)	0.93
GSTP1(Val / Val) and TLR2(Ins / Ins)	20	9		1(reference)		
GSTP1(Val / Val) and TLR2(Ins / Del)	14	6	0.06	1.17	(0.35 – 3.9)	0.8
GSTP1(Ile / Ile) and TLR2(Ins / Del)	22	11		1(reference)		

* ***Confidence interval***

Helicobacter pylori in 309 patients, and no found association of this polymorphism with the risk of ulcer gastric, duodenal ulcers and gastritis.Taken together, our data suggest that deletion -196 to -174 of the promoter of the TLR2 gene region was not enough to establish a correlation of polymorphism as a risk factor for infections that affect individuals with sickle cell disease. Possibly it is explained by numerous genetic variations in the pathogens recognition system, responsible for specific differences [37], and also because of the wide range of functionally relevant genetic alterations of the innate immune system [38].

It is necessary to search simultaneously for other candidate genes such as those encoding receptors that interact directly in the formation of heterodimers with TLR2 (TLR1, TLR6, and CD14) and protein signaling pathways, to characterize the profile of severe infections. For example, the presence of CD14 enhances the efficiency of recognition of TLR2-specific ligands [39].

Conclusions

The genotypes Ile/Val and Ins/Ins related to GSTP1 and TLR2, respectively, were the most frequent in this study. No association was found between GSTP1 (Ile/Val) and TLR2 (Del/Del) variant genotypes and increased risk of infections in sickle cell anemia.

Declaration of interest

None

Author contributions

Géssyka Jerônimo Silva: Formal analysis, investigation; *Romério Alencar de Oliveira Filho*: Formal analysis, investigation; *Igor de Farias Domingos:* Formal analysis, investigation; *Rodrigo Marcionilo de Santana:* Writing - review & editing; *Thais Helena Chaves Batista*: Writing - review & editing; *Aderson da Silva Araújo:* Conceptualization, Funding acquisition; *Marcos André Cavalcanti Bezerra:* Methodology, Supervision; *José Luiz de Lima Filho*: Funding acquisition; *Danyelly Bruneska Gondim Martins*: Methodology, Supervision; *Rosângela Ferreira Frade de Araújo*: Methodology, Project administration, Roles/Writing - original draft.

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