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Review

The glutathione s-transferases (GSTS) gene polymorphisms in colorectal cancers

[1]Daciana N. Chirila, [2]Mihaela D. Chirila, [3]Smaranda A. Istoan, [1]Bogdan V. Micu, [1]Mihai S. Muresan, [3]Daniel Gligor, [1]Tudor R. Pop

[1] Department of Surgery, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2] Department of Medical Disciplines, Oradea University, Faculty of Medicine and Pharmacy, Oradea, Romania; [3] Vth Surgical Clinic, Cluj-Napoca County Hospital, Cluj-Napoca, Romania.

Abstract. The glutathione S-transferases (GSTs) are important enzymes linked with detoxification properties of the cells, protecting them against multiple exogenous and endogenous substances, catalyzing the reactions of glutathione with a lot of substances, including those with genotoxic properties. There are seven human cytosolic GSTs classified into 7 classes (designated with Greek letters α, ζ, θ, μ, π, ς, τ, ω) and 6 isozymes of a group of membrane-associated family of proteins from classes I, II, and IV of the MAPEG (membrane-associated proteins in eicosanoid and glutathione metabolism). The individuals carrying a dual absent genotype of GSTM1 and GSTT1 genes have a complete absence of the corresponding enzymes activity; in the case of other GSTs enzyme activity may decrease and this may lead to malignant alteration. Our objective was to review data concerning the involvement of GST polymorphisms associated with the development of colorectal cancers. Although there have been many conflicting reports regarding this relationship, the current evidence indicates that some GST genotypes are associated with an increase in the risk of colorectal cancers depending on different ethnicities.

Key Words: colorectal cancer, colorectal neoplasms, colorectal malignant tumors, GST genes polymorphisms.

Corresponding Author: M. Chirila, email: cristimihachirila@yahoo.com

Introduction

Colorectal cancer

It was calculated that the lifetime probability of being diagnosed with an invasive cancer for men is higher than for women (42% versus 38%) (Siegel et al 2016). In 2016 the CRC (colorectal cancer) incidence rate estimations were that these tumors occupied the 3rd place in men and also in women (8% each), the 4th place for both sexes (after lung, breast and prostate cancer) in the USA. Because of the mortality rates, the CRC occupied the 3rd place in both men and women, but the 2nd place for both sexes (Siegel et al 2016). The purposes behind an expanded weakness in men are not surely knew, but rather there are numerous elements involved, among them the natural exposures, endogenous hormones, and possibly different complex cooperation between these impacts.

The Glutathione S-transferases (GSTs) catalyze the reaction between glutathione and electrophilic compounds, increasing their water solubility in order to help their excretion as toxic compounds (Hayes et al 2005). Nowadays we consider that the GSTs form the main detoxification system for resistance to cell damage. Polymorphisms in GSTs are able to modify the detoxification procedure or even stop it, and this process leads to accumulation of carcinogen precursors. As a result, these can activate or convert to toxic substances, and increase susceptibility to tumors (Chen et al 2017). There are seven classes of human cytosolic GSTs: Alpha, Mu, Pi, Sigma, Theta, Omega, and Zeta (Armstrong 1997; Hayes&McLellan 1999; Board et al 2000). The Kappa GST is a mitochondrial class, found also in peroxisomes (Morel et al 2004; Robinson et al 2004). The GSTs have isoenzymes that share 75%-95% protein sequence identity (Pearson et al 1993) but members of different classes have less than 30% protein sequence identity.

Implication of GST polymorphisms in colorectal cancer (CRC)

An early study (Cotton et al 2000) did not find link of the absent GSTM1 and GSTT1 genotype with risk for CRC; other later studies showed that there was not a significant increased risk associated with the absence of GSTM1 enzyme (Ye&Parry 2003), but association with the absent GSTT1 genotype (Chen et al 2005).

A 2009 meta-analysis of 27 case-control studies (12 for GSTM1 polymorphism, 8 for GSTT1, 7 for mEH3, mEH4, and 10 for NAT2) studying the interactions between genetic polymorphisms, smoking, and colorectal adenoma or cancer found a small interaction between the GSTT1 absent genotype and smoking only for the risk of colorectal adenoma (Raimondi et al 2009).

A 2010 meta-analysis (Economopoulos et Sergentanis 2010) consisting of 44 studies for GSTM1 (11,998 colorectal cancer cases, 17,552 controls), 34 studies for GSTT1 (8596 cases, 13,589 controls), 19 studies for GSTP1 (5421 cases, 7671 controls) and four studies for GSTA1 polymorphism (1648 cases, 2039 controls) revealed: the modified GSTM1 genotype (complete absence) offered an increased CRC risk in a Caucasian race

population (pooled OR=1.150), but not in a Chinese population (pooled OR=1.025). Analyzing the influence of a null genotype for GSTT1, this was linked to the risk for CRC in a Caucasian population (pooled OR=1.312), but there was no significant association in a Chinese population (pooled OR=1.068). When both genes were absent it was found an additional risk for CRC only for a Caucasian population; the variant GSTP1 genotype Ile105Val and the variant polymorphism of GSTA1 *A/*B showed no significant associations with CRC risk.

A small increased risk of colorectal cancer has been found (OR was 1.23) in patients with a GSTT1 null genotype, especially for Caucasian populations (OR = 1.39/ 10 studies) and Asian populations (OR = 1.23/ 5 studies) in a 2010 meta-analysis (Liao et al 2010) of 23 case-control studies with 11,057 individuals (5,058 cases and 5,999 controls).

The people with null genotype of GSTT1 (OR=1.09) produced an augmented risk for CRC in Asians in a 2011 meta-analysis of 13 studies with 4,832 CRC cases and 7,045 controls (Xu et al 2011).

A 2012 Chinese meta-analysis involving 9,553 individuals, 3,130 being patients with CRC from 19 studies found for each null genotype of GSTM1, GSTT1 and both GSTM1+GSTT1 as not being risk factors in CRC in a Chinese population (Wang et al 2012).

A 2012 meta-analysis (Zhong et al 2012) of 12 case-control studies from an Asian population with 4,517 CRC cases and 6,607 controls revealed that the variant of double null allele of GSTT1 determined a rise of the risk for CRC (OR = 1.10).

In the same year another study found that GSTM1, GSTP1 AG, and GSTT1 (OR=1.21) variants are associated with modest but significant intensifications of the CRC risk (Ramsay et al 2012).

A 2013 meta-analysis of 506 case-control studies found that the variant of absent GSTM1 genotype (OR=1.17) was highly linked with an amplified risk for CRC, cancer of the prostate, breast, bladder, lung, stomach, head and neck, nasopharyngeal carcinoma and acute lymphocytic leukemia. Also, the variant of absent GSTT1 genotype (OR=1.16) presented an increased risk for CRC and cancer of the breast, lung, stomach, head and neck and other cancers. In case of dual GSTM1+GSTT1 null genotypes, the smokers were associated with an enhanced cancer risk (Fang et al 2013).

A 2013 meta-analysis (Qin et al 2013) consisting of 46 case-control studies with 15,373 CRC cases and 21,238 controls discovered an increased risk of CRC associated with a GSTT1 null genotype (OR=1.21, 95% CI=1.10-1.33), especially for rectal cancers (OR=1.28, 95% CI=1.01-1.64), but not in colon cancer (OR=1.27, 95% CI=0.94-1.73). The study showed no correlation between smoking, Dukes stages and differentiation of CRC. They also underlined an increased risk for CRC in patients with null genotypes of GSTM1 and GSTT1 (OR=1.55).

A recent meta-analysis (Song et al 2014) investigating 23 retrospective studies (with 6,981 cases and 8,977 controls) found that the variant Ile105Val of GSTP1 heterozygotes but not homozygotes had a significant augmented risk of CRC.

20 studies analyzed in a 2014 meta-analysis (Xu et al 2014) with 10471 individuals, from which 4770 were CRC patients revealed a significantly increased cancer risk (OR = 1.20, even more than that for Caucasian population OR=1.32) for the variant GG vs. AA of GSTO2, but not for GSTO1 polymorphism; also this variant of GSTO2 was linked with an augmentation of breast cancer risk (OR = 1.37).

A 2015 meta-analysis (Li et al 2015) of 33 case-control studies in Asian populations with 8502 colorectal cancer patients and 13699 controls found GSTM1 null variant associated with an increased risk for CRC in Asians.

The GSTA1 polymorphisms showed an association with an increased risk for CRC in Caucasians for the B allele (-567G, -69T, -52A) compared to the common GSTA1 A allele (-567T, -69C,-52G) in patients with BB vs. AA (OR=1.35) and BB vs. AA+AB (OR=1.39) in a recent meta-analysis of 15 studies (Deng et al 2015).

The GSTO2 NN genotype seems to increase the risk of CRC in persons with a positive family history for cancer in first degree relatives (Masoudi et al 2011).

Discussion

Data from year 2012 showed an incidence of CRC in men (10.0% of the total number of cancer cases) and in women (9.2% of the total number of cancer cases), determining that CRC was the third more common cancer in men and second one in women in 2012 (Ferlay et al 2013), with more than half of the cases occurring in higher developed regions. The recorded mortality for CRC was lower (under 10% of the total number of deaths from cancer) with more than half deaths in poor developed countries of the world. It is important to mention that the peak estimated mortality rates in both sexes were in Eastern and Central Europe (20.3/100,000 in men, 11.7/100,000 in women), at the bottom being the people in Western Africa (3.5/100,000 in men and 3.0/100,000 in women). The GSTs detoxify carcinogens including heterocyclic aromatic amines found in cooked meat and polycyclic aromatic hydrocarbons in cigarette smoke, which are associated with increased risk of colorectal cancer (de Jong et al 2002).

There is an increasing interest in the role that polymorphisms in phase I and phase II detoxification enzymes may play in the etiology and progression of diseases. Polymorphisms which reduce or eliminate these enzyme detoxification activities may increase a person's susceptibility to diseases including colorectal cancer. The GSTs have been divided based on their amino acid sequence homology in combination with other criteria, such as tertiary structure similarity, substrate specificity, and immunological identity (Mannervik et al 1992). Human GSTs are divided into three main families: cytosolic (Mannervik 1985), mitochondrial, and membrane-bound microsomal. The cytosolic GSTs are a family of intracellular enzymes divided in at least seven major groups (Hayes et al 2005) with correspondent subunits: Alpha (A1, A2, A3 e A4), Pi (P1), Mu (M1, M2, M3, M4 e M5), Theta (T1 and T2), Zeta, sigma (S), and omega (O). Table 1 presents the genetic location and examples of relation with different tumors.

The GSTs, xenobiotic-processing compounds, constitute an essential line of guard against an assortment of cancer-causing agents. The GST enzymes conjugate hydrophobic and electrophilic compounds with reduced glutathione. The genetic variants may be more or less efficient in metabolizing carcinogens, contributing to individual disease susceptibility depending on the substrate metabolized. Several studies have shown influence of GSTs polymorphism in cancer susceptibility due to their role

Table 1. The cytosolic classes of GSTs with chromosomal site and neoplastic disease they may interact.

GST Class	Chromosomal location	Implication in cancer disease
GSTA1	6p12.1	defense activity against oxidative stress (Zhao et al 1999); endodermal sinus tumor of ovary; ovarian yolk sac tumor
GSTM1	1p13.3	Prostate cancer (Mo et al 2009; Liu et al 2013; Malik et al 2016); lymphoma (Atanaskovic et al 2016); acute myeloid leukemia (Das et al 2009); oral cancer (Zhang et al 2011); cervical cancer (Wang et al 2011)
GSTP1	11q13	Bladder cancer (Safarinejad et al 2013); breast cancer (Lu et al 2011); esophageal cancer (Lin et al 1998)
GSTT1	22q11.2	Prostate cancer (Liu et al 2013); cervical cancer (Kim et al 2000); acute leukemia (Ye et Song 2005); breast cancer (Sergentanis et Economopoulos 2010)
GSTK1	7q34-35	obesity, diabetes (Shield et al 2010)
GSTO1	10q25	liver and breast cancer (Marahatta et al 2006) and CRC (Massoudi et al 2011)
GSTZ1	14q24.3	No influence of the risk for gastric cancer (Karakas-Celik et al 2014) or breast cancer (Saadat et al 2012; Andonova et al 2010)

in modulation of the biological effects of the carcinogens. Now we consider that the GST gene polymorphisms may exert an effect on the functioning of GST enzymes by changing not only the level of gene expression but also the activity of the protein itself. Through this the polymorphisms influence the cleansing of carcinogens, and also the DNA impairment; in this way, the GSTs polymorphisms may have an indirect consequence on the risk of progress of cancer disease (Gong et al 2012). GSTs may interact with different proteins and thus they can modulate signaling pathways that control cell proliferation, differentiation and apoptosis (Singh 2015).

Both GSTM1 and GSTT1 may have polymorphisms consisting of absence of one or both alleles. In case of a null genotype it will be no enzyme activity and this may cause an impossibility of removing many electrophilic carcinogens, which may increase the risk of somatic mutations and finally cancer. The null GSTM1 genotype was found in 48%-51% of Japanese, in 35%-63% of Chinese, in 33%-36% of Asian Indians, in 50% of Caucasians and in 22%-35% of Africans (Rebbeck 1997). Up to 20% of Caucasians and 80% of Asians do not have the enzyme GSTT1 (Landi 2000).

There are two GSTP1 polymorphisms which substantially reduced GSTP1 enzyme activity toward several substrates, including both chemotherapy agents carcinogens (Hayes & Strange 2000). One of them is characterized by a change from isoleucine (Ile) to valine (Val) in position 105 in exon 5 of the gene; the other one consists of another change in exon 6, this time an alanine (Ala) to Val (Ala114Val). These modified genotypes will lower the levels of metabolic activity of GSTP1 (Harris et al 1998). The frequency of the modified Ile105Val variant can be found in 31% of Caucasians, 54% of African Americans and 17% of Asians; 10% of Caucasians have the Ala114Val variant, but it was not found in Asians and African Americans (Packer et al 2006).

Another idea may be the study of the GSTs polymorphisms in patients with multiple primary cancers of the same or different digestive segments, as it was noticed in a small study with multiple primary CRCs (Chirila et al 2013).

In the ongoing years the overexpression of some GSTs, specifically GSTP1-1, to both characteristic and attained resistance from different fundamentally irrelevant anticancer medications, inspired the inquiry of GST inhibitors and GST-enacted cytotoxic prodrugs (Ruzza et al 2009). The inhibitors are used to modulate tumor cell drug resistance, as sensitizers to therapeutically directed oxidative stress, also to enhance cell proliferation (Mahajan & Atkins 2005).

The relationships between GST polymorphisms and the development of colorectal cancers enjoyed a lot of attention and spark our interest in the last decade. The studies revealed an association with genetic differences between human races, that is why it is difficult to comprehend and evaluate the impact of all the factors related to life style or exposure to different environmental factors.

Conclusions

Even if some results are conflicting, the larger studies showed that GSTs polymorphisms (GSTM1, GSTA1, GSTT1, GSTO2, and variant of GSTP1) are risk factors for CRCs in Caucasians and also in Asians. Future investigations may additionally survey the conceivable quality and quality natural cooperation in this relationship with colorectal growth chances.

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Authors

•Daciana N. Chirila, Department of Surgery, „Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, 5th Surgical Clinic, 11th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: dacianachirila@gmail.com

•Mihaela D. Chirila, Department of Medical Disciplines, Oradea University, Faculty of Medicine and Pharmacy, Oradea, Bihor County, Municipal Clinical Hospital „Dr. Gavril Curteanu" Oradea, 12th Corneliu Coposu Street, 410469, Oradea, Bihor, Romania, EU, email: cristimihachirila@yahoo.com

•Smaranda A. Istoan, 5th Surgical Clinic, Cluj-Napoca County Hospital, 11th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: smarandaistoan@yahoo.com

•Bogdan V. Micu, Department of Surgery, „Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, 5-th Surgical Clinic, 11-th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: micubogdan@yahoo.com

•Mihai S. Muresan, Department of Surgery, „Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, 5-th Surgical Clinic, 11-th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: mihai.stefan.muresan@gmail.com

•Daniel Gligor, 5th Surgical Clinic, Cluj-Napoca County Hospital, 11th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: danielgligor02@yahoo.com

•Tudor R. Pop, Department of Surgery, „Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, 5th Surgical Clinic, 11th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: poptudor_2003@yahoo.com

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