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ORIGINAL ARTICLE

Impact of the Ser326Cys polymorphism of the OGG1 gene on the level of oxidative DNA damage in patients with colorectal cancer

Authors' Contribution:
A–Study Design
B–Data Collection
C–Statistical Analysis
D–Data Interpretation
E–Manuscript Preparation
F–Literature Search
G–Funds Collection

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ABSTRACT:

As a result of reactive oxygen species operation, cell damage occurs in both cellular organelles and molecules, including DNA. Oxidative damage within the genetic material can lead to accumulation of mutations and consequently to cancer transformation. OGG1 glycosylase, a component of the Base Excision Repair (BER) system, is one of the enzymes that prevents excessive accumulation of 8-oxoguanine (8-oxG), the most common compound formed by oxidative DNA damage. In case of structural changes of OGG1 resulting from polymorphic variants, we can observe a significant increase in the concentration of 8-oxG. Linking individual polymorphisms to DNA repair systems with increased risk of colorectal cancer will allow patients to be classified as high risk and included in a prophylactic program.

The aim of the study was to determine the level of oxidative DNA damage and to analyze the distribution of Ser326Cys polymorphism of the OGG1 gene in a group of patients with colorectal cancer and in a control group in the Polish population.

Material and methodology. DNA was isolated from the blood of 174 patients with colorectal cancer. The control group consisted of 176 healthy individuals. The level of oxidative damage was determined by analyzing the amount of 8-oxguanine using the HT 8-oxo-dG ELISA II Kit. Genotyping was performed via the TaqMan method.

Results. The obtained results indicate that Ser326Cys polymorphism of the OGG1 gene increases the risk of RJG and is associated with significantly increased levels of 8-oxoguanine.

Conclusions. Based on the results obtained, we conclude that Ser326Cys polymorphism of the OGG1 gene may modulate the risk of colorectal cancer by increasing the level of oxidative DNA damage.

KEYWORDS: colorectal cancer, OGG1, 8-oxoguanine, DNA repair, oxidative damage

INTRODUCTION

Despite improved diagnostic programs and increasingly advanced treatments, the incidence of colorectal cancer (CRC) continues to increase. In addition, direct causes of disease development still remain unknown, and the spectrum of factors contributing to the modulation of its risk is becoming increasingly widespread. As with other types of malignant tumors, the most important role seems to be the combination of genetic predispositions with the influence of environmental factors. Among the latter, oxidative damage generated by oxidative stress are well recognized factors. Tobacco use and an inappropriate diet can contribute to increased levels of reactive oxygen species (ROS) which, interacting with DNA, lead to oxidative DNA damage. Oxidative damage within the genetic material can lead to accumulation of mutations and consequently, to cancer transformation. Chronic aggressive ROS activity on the mucous membrane of the large intestine causes chronic inflammation, which gradually modifies the normal epithelial structure leading to greater dysplasia of the tissue. This histological change is a precursor of CRC [1]. The effect of reactive oxygen species on DNA is an oxidative modification of the nitrogen base, and the most commonly modified base is 8-oxoguanine, whose increased level is observed in the cells of many types of cancer [2, 3, 4]. In cells with properly functioning DNA repair systems and antioxidant mechanisms, many pathways prevent excessive ROS accumulation, and if DNA damage is already present, it removes 8-oxG. Responsible for this, among others is OGG1 glycosylase [5]. However, in the event of reduced activity, 8-oxG accumulation is expected to eventually lead to cancer transformation.

The aim of this work was to evaluate the effect of Ser326Cys polymorphism of the OGG1 gene on the level of oxidative DNA damage in patients with colorectal cancer by analyzing the 8-oxoguanine level.

MATERIAL AND METHODS

Experimental Material - DNA was isolated from peripheral blood lymphocytes from samples of 174 unrelated patients. All patients have histopathologically confirmed colorectal cancer. The study group consisted of 93 males and 81 females (mean age 63 years ± 7). The control group consisted of 176 age-related subjects who had no cancer.

Methods - DNA isolation was carried out with a commercial QIAamp DNA Blood Mini Kit for isolation of high molecular-weight

DNA (Qiagen). Distribution of Ser326Cys polymorphic variants of the OGG1 gene was investigated using the TaqMan method. Level 8-oxoguanine was determined in DNA using the HT 8-oxo--dG ELISA II Kit (R & amp; D Systems).

STATISTICAL ANALYSIS

The number of genotypes received was compared with the expected value under the Hardy-Weinberg law. The significance of differences between allele frequencies and genotypes for individual groups was assessed using the $\chi 2$ test. The risk of occurrence of the event was assessed by means of multivariate regression analysis (odds ratio, OR) with an appropriate confidence interval (CI 95% - confidence interval 95%).

RESULTS

Table 1 presents an analysis of the distribution of Ser326Cys polymorphic variants of the OGG1 gene and their correlation with the modulation of the risk of colorectal cancer. Studies indicate that the Ser326Cys genotype of the OGG1 gene may increase the risk of CRC (OR 1.7967 (1.138-2.836), p = 0.011). Figure 1 shows the level of 8-oxoguanine in patients with CRC and in the control group. In addition, the 8-oxG levels for each of the Ser326Cys polymorphic variants of the OGG1 gene are listed. A statistically significant increase in 8-oxG levels was observed for the Ser326Cys genotype, both in the CRC and control group.

Tab. I. Correlation of Ser326Cys polymorphism of OGG1 gene with the occurrence of colorectal cancer.

GENOTYPE/ ALLELE	PATIENTS N=174	CONTROLS N=176*	OR (95% CI)	P
Ser/Ser	52	72	1 (ref)	-
Ser/Cys	109	84	1.7967 (1.138-2.836)	0.011
Cys/Cys	13	20	0.939 (0.586-1.505)	0.791
Ser	213	228	1 (ref)	-
Cys	135	124	1.079 (0.928-1.256)	0.330

* genotype distribution in Hardy-Weinberg equilibrium, x^2=0.543

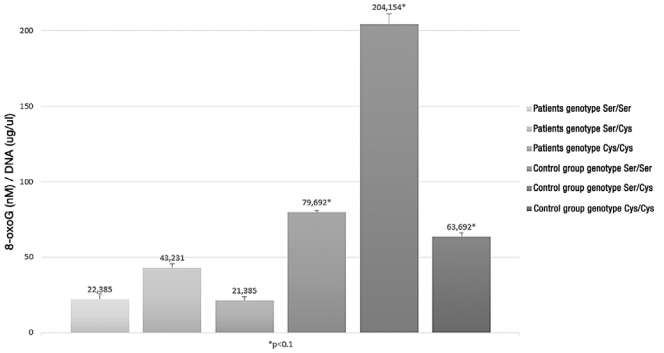

Fig. 1. 8-oxoguanine levels in patients with CRC and control group.

DISCUSSION

Reduced efficiency of DNA repair mechanisms is a recognized factor in the increased risk of cancer [6, 7] including colorectal cancer [8, 9] and is considered as a new therapeutic approach to treating cancer [10]. One of the mechanisms underlying the increase in risk may be the accumulation of reactive oxygen species, which also contribute significantly to the neoplasmic process [11, 12]. The aim of this study was to evaluate the influence of polymorphic variants of the Ser326Cys OGG1 gene on the modulation of the risk of CRC occurrence while simultaneously analyzing the level of oxidative damage in the DNA. The results show that the Ser326Cys genotype of the OGG1 gene is associated with an increased risk of CRC, which is consistent with the available literature [13, 14]. At the same time, our previous studies also show that the level of oxidative damage is significantly higher and the efficiency of their repair is much lower in patients with CRC [15, 16]. However, there is no literature that would point to a direct correlation between the polymorphisms and oxidative damage levels, so far, only the relationship between 8-oxG levels in patients and the risk of cancer [17]. Our results show that 8-oxoguanine levels are higher in patients with CRC than in the control group. At the same time, intra-group analysis by genotype indicates that for the genotype of Ser326Cys of the OGG1 gene, the 8-oxG level is significantly higher than for the other two genotypes, both in the control group and in the patients' group. This indicates the probable underlying mechanism of DNA damage in this case, that is, caused by the decreased efficiency of OGG1 glycosylase 8-oxoguanine accumulation in the genetic material. The coexistence of this process with increased oxidative stress may lead to an increased risk of malignant transformation. The transformation process itself is an extremely complex and complicated one, so further research is needed to fully understand the role that particular polymorphisms of DNA repair genes play in it. However, we postulate that understanding this role will allow for more effective diagnostics of people with increased risk of CRC and to include them in prevention programs.

REFERENCES:

1. Ribeiro, M. L., Priolli, D. G., Miranda, D. D., Arçari, D. P., Pedrazzoli, J., & Martinez, C. A. (2008). Analysis of oxidative DNA damage in patients with colorectal cancer. Clinical colorectal cancer, 7(4), 267-272.
2. Paz-Elizur, T., Krupsky, M., Elinger, D., Schechtman, E., & Livneh, Z. (2005). Repair of the oxidative DNA damage 8-oxoguanine as a biomarker for lung cancer risk. Cancer Biomarkers, 1(2-3), 201-205.
3. Paz-Elizur, T., Ben-Yosef, R., Elinger, D., Vexler, A., Krupsky, M., Berrebi, A., ... & Livneh, Z. (2006). Reduced repair of the oxidative 8-oxoguanine DNA damage and risk of head and neck cancer. Cancer research, 66(24), 11683-11689.
4. Park, J., Chen, L., Tockman, M. S., Elahi, A., & Lazarus, P. (2004). The human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) DNA repair enzyme and its association with lung cancer risk. Pharmacogenetics and Genomics, 14(2), 103-109.
5. Nakabeppu, Y. (2014). Cellular levels of 8-oxoguanine in either DNA or the nucleotide pool play pivotal roles in carcinogenesis and survival of cancer cells. International journal of molecular sciences, 15(7), 12543-12557.
6. Torgovnick, A., & Schumacher, B. (2015). DNA repair mechanisms in cancer development and therapy. Frontiers in genetics, 6.
7. Orlow, I., Park, B. J., Mujumdar, U., Patel, H., Siu-Lau, P., Clas, B. A., ... & Dominguez, G. (2008). DNA damage and repair capacity in patients with lung cancer: prediction of multiple primary tumors. Journal of Clinical Oncology, 26(21), 3560-3566.

8. Peltomäki, P. (2001). Deficient DNA mismatch repair: a common etiologic factor for colon cancer. Human Molecular Genetics, 10(7), 735-740.
9. Marra, G., & Boland, C. R. (1996). DNA repair and colorectal cancer. Gastroenterology Clinics, 25(4), 755-772.
10. Kelley, M. R., Logsdon, D., & Fishel, M. L. (2014). Targeting DNA repair pathways for cancer treatment: what's new?. Future Oncology, 10(7), 1215-1237.
11. Sreevalsan, S., & Safe, S. (2013). Reactive oxygen species and colorectal cancer. Current colorectal cancer reports, 9(4), 350-357.
12. Lin, J., Chuang, C. C., & Zuo, L. (2017). Potential roles of microRNAs and ROS in colorectal cancer: diagnostic biomarkers and therapeutic targets. Oncotarget, 8(10), 17328.
13. Lai, C. Y., Hsieh, L. L., Tang, R., Santella, R. M., Chang-Chieh, C. R., & Yeh, C. C. (2016). Association between polymorphisms of APE1 and OGG1 and risk of colorectal cancer in Taiwan. World journal of gastroenterology, 22(12), 3372.
14. Das, S., Nath, S., Bhowmik, A., Ghosh, S. K., & Choudhury, Y. (2016). Association between OGG1 Ser326Cys polymorphism and risk of upper aero-digestive tract and gastrointestinal cancers: a meta-analysis. SpringerPlus, 5(1), 227.
15. Kabzinski, J., Przybylowska, K., Dziki, L., Dziki, A., & Majsterek, I. (2015). An association of selected ERCC2 and ERCC5 genes polymorphisms, the level of oxidative DNA damage and its repair efficiency with a risk of colorectal cancer in polish population. Cancer Biomarkers, 15(4), 413-423.
16. Kabzinski, J., Mucha, B., Cuchra, M., Markiewicz, L., Przybylowska, K., Dziki, A., ... & Majsterek, I. (2015). Efficiency of base excision repair of oxidative DNA damage and its impact on the risk of colorectal cancer in the polish population. Oxidative medicine and cellular longevity, 2016.
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Competing interests:
The authors declare that they have no competing interests.

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