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MDR 1 C3435T Gene Polymorphism in Colorectal Cancer

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ABSTRACT

Introduction: Colorectal cancer is one of the most frequent malignancies. Single nucleotide polymorphism may contribute to an increased or decreased cancer risk. The ABCB1/MDR1 gene seems to play an important role in tumor progression. The aim of this study is to associate genotypes and/or alleles of the polymorphism with different phenotypes in CRC patients.

Material and Methods: A total of 102 CRC patients were recruited. All the individuals were genotyped for MDR1 C3435T polymorphism.

Results: The median survival in CC genotype carriers - CRC women were 1 year whereas in CT and TT group it was 6 years and 7 years. These results suggest that CC genotype is associated with a lower survival rate in CRC women (P=0.04). Significantly higher levels of CEA were found in the CC genotype carriers -CRC women (median CEA 7.9, range 1.3-20.5 μg/l) compared to the CT group (median CEA 1.6; range 0.5-12.1 μg/l) and TT group (median CEA 0.5, range 0.5-0.8 μg/l). P=0.06. The representation of the CT genotype is significantly higher in the T3 group of CRC women. OR for the CT genotype is 12; 95%CI=1.10-1.31; P=0.05. The CT+TT genotype carriers were observed 15 times more frequently in women with low resection (OR=15; 95% CI 1.14-198.05; sensitivity=1, specificity=0.5; power test =0.622; P=0.01).

Discussion: Our genotype-phenotype study has brought new data and can also serve for a better understanding of this matter in the future. Our results were significant only in females, although the difference in genotypes/alleles between males and females was not significant. A larger sample would be needed to confirm our results.

Keywords: Colorectal Cancer; MDR1; Gene Polymorphism; Genotype Phenotype Study

Abbreviations: CRC: Colorectal Cancer; SNP: Single Nucleotide Polymorphism; MDR1: Multidrug Resistance Gene 1; P-gp: P-Glycoprotein; CEA: Carcinoembryonic Antigen; OR: Odds Ratio; CI: Confidential Interval

Introduction

Colorectal cancer (CRC) is one of the most frequent malignancies and is the main reason for the high mortality ratio among different types of cancer in the Western World [1]. The GLOBOCAN 2020 indicates that there were 19.3 million new cases of cancer and almost 10 million deaths from cancer in 2020. Overall, colorectal cancer ranks third in terms of incidence, but second in terms of mortality. There is an approximately 9-fold variation in colon cancer incidence rates by world regions, with the highest rates in European regions, Australia/New Zealand, and Northern America [2].

Malignant tumors represent a quarter of all deaths in the Czech Republic and the second most common cause of death after cardiovascular diseases. In the Czech Republic, there were 6970 new cases of colorectal cancer diagnosed in 2020 from which 4077 (58%) accounts for men and 2893 (42%) for women. Mortality for colorectal cancer was 3435 persons: 2013 (59%) cases in men and 1422 (41%)

in women [3]. These numbers illustrate why the research regarding colorectal cancer is so important for health care professionals and why any data helping with earlier diagnosis and better prediction of prognosis is needed.

Colorectal carcinogenesis is a complex, multistep, and multifactorial process that is triggered by the interaction of many factors. These factors could be influenceable such as lifestyle and dietary habits but also not influenceable like genetic susceptibility [2,4]. Several studies prove that single nucleotide polymorphism (SNP) of some genes may contribute to an increased or decreased cancer risk [5,6]. Among those SNPs, the ABCB1/MDR1 gene seems to play an important role in tumor progression [7]. The multidrug resistance gene 1 (MDR1), located on chromosome 7q21.1, encodes an ATP transmembrane glycoprotein, P-glycoprotein (P-gp). This protein acts as an efflux pump of xenobiotics and also drugs such as chemotherapeutics. P-gp is expressed in healthy cells of intestine, liver, brain, kidney, and is responsible for decreasing intracellular xenobiotic accumulation. It is believed that P-gp also plays a role in regulating cell death, immune responses, differentiation, and proliferation [8]. In the physiological state, epithelial cells in the colon have a high concentration of P-gp. However, polymorphism in the MDR 1 gene leading to changed expression can weaken its desired effect in defense against xenobiotics and lead to increased risk of developing CRC [9,10]. On the other side, chemotherapy resistance of tumors can be modified by function of the gene [11].

The ABCB1/MDR1 gene is polymorphic and there are approximately 48 SNPs found in all of his 28 exons [12]. Polymorphism in exon 26 (rs1045642, C3435T) causes a silent mutation that seems to be associated with altered protein function [13]. The C3435T is one of the polymorphisms that was studied in multiple diseases and also in CRC. The aim of this study is to associate genotypes and/or alleles of the polymorphism with different phenotypes in CRC patients.

Material and Methods

Subjects

This study was conducted on 102 patients with diagnosed colorectal cancer. The study group included 79 men and 23 women with an average age of 69.4 years (SD 9.7). All patients were after surgical treatment with resection of the CRC lesion. The TNM classification according to UICC (1978) was determined in every patient. clinical data including age, gender, BMI, survival, smoking, and some tumor markers were collected.

Genetic Analysis

The genetic examination was performed at the Department of Pathological Physiology, Masaryk University Brno. Genomic DNA was extracted from peripheral T lymphocytes using a standard proteinase K technique. Patients were genotyped for C3435T polymorphism using polymerase chain reaction and restriction analysis. For this purpose, the MDR-11 and MDR-12 primers were used. For restrictive analysis, the amplified DNA sequence was digested by an MBO1 restriction endonuclease. For final detection of obtained fragments was used electrophoresis on 3% agarose gel. Obtained fragments were 197bp for the T/T genotype, 162bp, and 35bp to the C/C genotype and 197bp, 162bp, and 35bp to the C/T genotype.

Statistical Analysis

The distributions of genotype and allelic frequencies and their differences were calculated using χ 2 tests. Consistency of genotype frequencies with the Hardy–Weinberg equilibrium was tested using a χ 2 test on a contingency table of observed versus predicted genotype frequencies. Odds ratio (OR) and 95% confidence intervals were calculated to estimate the risks related to detected polymorphisms. To calculate the significance of OR, Fisher's exact test was used. The corrected P values for multiple comparisons (Pcorr) were calculated by Holm's test when necessary. The program package Statistica v. 12.0 (Statsoft Inc., Tulsa, OK, USA) was used.

Results

Basic demographic data describing CRC patients enrolled to the study are presented in Table 1. In the women group of our patients, the survival rate was significantly different according to MDR-1 genotypes (Table 2). In the group of MDR-1 CC genotype, the median survival was 1 year whereas in CT and TT group the median survival was 6 years and 7 years, respectively. P-value equals 0.04. These results suggest that CC genotype is associated with a lower survival rate and therefore could serve as a negative prognostic factor. Interestingly, the result seems to correspond to significantly higher levels of carcinoembryonic antigen (CEA) which were found in the CC genotype carriers (median CEA 7.9, range 1.3-20.5 μg/l) compared to the CT group (median CEA 1.6; range 0.5-12.1 μg/l) and TT group (median CEA 0.5, range 0.5-0.8 μg/l). P-value equals 0.06.

Table 1: Demographic data.

	CRC men	CRC women	P
Age (median, range) years	69, 47-88	72, 48-88	NS
Survival Y/N	59/18 (77%)	17/6 (74%)	NS
Survival (median, range) months	6, 0-7	6, 0-7	NS
BMI (median range) kg/m^2	26, 0-41	27, 16-35	NS
Smoking Y/N	26/52 (33%)	3/20 (13%)	0.05
Surgery type 1/2/3*	32/30/13	6/16/1	02:00.0
MDR1 genotype CC/CT/TT	17/41/16	3/17/3	Pg=0.286 Pa=0.936

Note: Surgery type 1/2/3*: 1-Miles´, 2-low resection, 3-other; Pg=probability of a difference in genotype distribution, Pa=probability of a difference in allelic frequencies.

Table 2: Survival rate after surgery in CRC women.

MDR-1 genotype	Survival N	Survival Minimum (years)	Survival Maximum (years)	Survival Median (years)
CT	17	0	7	6
CC	3	0	6	1
TT	3	6	7	7

In CRC women group, we observed also a different proportion of T staging (TNM classification in different MDR1 genotype carriers (Table 3). The representation of the CT genotype is significantly higher in the T3 group compared to T1 and T2. Odds ratio (OR) for the CT genotype is 12; 95% confidential interval (CI)=1.10-1.31; P=0.05 which means that the CRC women with CT genotype are 12 times more likely to have a T3 tumor compared to other MDR1 genotypes carriers. The sensitivity of the test is 0.923 and specificity 0.5 with the power of the test equal to 0. 429.When we compared genotype distribution and/or allelic frequencies in MDR1 polymorphism in CRC women according to the type of surgery, a significant difference in genotype distribution was found between patents with Miles´s surgery compared to low resection (Table 4). The CT + TT genotype carriers were observed 15 times more frequently in the CRC women with low resection compared to those with Miles´ surgery (OR=15; 95% CI 1.14-198.05; sensitivity=1, specificity 0.5; power test =0.622; P=0.01, pcorr=0.05). In the male group of our patients, there were no statistically significant results regarding C3435T genotype variations and the risk of any phenotypes.

Table 3: TNM staging and MDR1 genotypes in CRC women.

TNM - T	MDR-1 CT	MDR-1 CC	MDR-1 TT	Row Totals
T1	1	1	1	3
T2	4	1	2	7
T3	12	1	0	13
All Grps	17	3	3	23

Table 4: Surgery types and MDR1 genotypes in CRC women.

Surgery type – CRC women	MDR-1 CT	MDR-1 CC	MDR-1 TT	Row Totals
Miles -1	3	3	0	6
Low resection 2	13	0	3	16
Others-3	1	0	0	1
All Grps	17	3	3	23

Discussion

Colorectal cancer, diagnosis covering malignant neoplasm occurring in the colon, and the rectum is a disease caused by multiple factors such as genetics, lifestyle, environment, and also socioeconomic status and their epigenetics relations [14]. While the Czech Republic is one of the countries with the highest incidence of CRC in the world [15], it is a convenient environment for conducting research on this matter. Correlation between the presence of different single nucleotide polymorphisms and the risk of colorectal cancer development and prognosis is being investigated in a large number of different genes [16]. MDR1 is among those being investigated extensively. One of the frequent polymorphisms analysed is C3435T in exon 26 of the MDR1 gene. A recent study indicated that polymorphism in exon 26 (rs1045642, C3435T) is associated with altered protein function [13]. In terms of altered function, it was found that Caucasians with the homozygous TT genotype of C3435T had a lower intestinal expression of P-gp [17]. According to another study Caucasian individuals with TT genotype aged under 50 years had the highest risk of developing CRC [18]. It should be noted that the relative contribution of genetic polymorphisms to the development of CRC may differ across ethnic groups. Some research suggested that there was no relationship between P-gp expression, genotype, and long-term prognosis [19]. Despite various research conducted on this topic, the possible role of MDR1 polymorphism in carcinogenesis of CRC remains unclear. While some studies found a link between ABCB1 C3435T polymorphisms and CRC risk [18, 20-23], others have come to conflicting results [24-27].

Due to intensive research activity in the field, a number of the meta-analysis could be done to clarify the role of C3435T polymorphism, but the results are inconsistent [28-30]. A meta-analysis published in 2013 containing a total of 11 339 patients suggested that ABCB1/MDR1 C3435T polymorphism is not related to colorectal cancer susceptibility [28]. Another meta-analysis conducted in 2017 which involved 4818 individuals demonstrated that C3435T polymorphism might be significantly associated with decreased risk of CRC for persons carrying a T allele in an Asian population [29]. Our genotype-phenotype study presenting results from genotype-phenotype study analyzing 102 patients diagnosed with CRC has brought new data and can also serve for a better understanding of this matter in the future. Our results were significant only in females, although the differences in genotypes distributions/ allelic frequencies between males and females were not significant. The results showed that the CC genotype could be associated with a worse survival rate along with higher CEA levels in women. According to our results, women with CT genotype are more likely to have locally advanced tumors marked as T3 in TNM classification. Because of the low number of women included in this study, there are statistical limits for all evaluations. A larger sample of individuals would be needed to confirm our results. Our results support the necessity of continuing research of genetic variability (polymorphisms) associations with phenotype characteristics of tumors.

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