

An association of the MCP-1 and CCR2 single nucleotide polymorphisms with colorectal cancer prevalence

Authors' Contribution:

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
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ABSTRACT:

The aim of the study: We evaluated the connection between the presence of the -2518 A/G MCP-1 as well as 190 G/A CCR2 polymorphic variants and colorectal cancer (CRC) occurrence.

Material and methods: Study group consisted of subjects with different stages of CRC as well as healthy controls. Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

Results: We observed an association between the colorectal cancer and the GG genotype of the -2518 A/G MCP-1 single nucleotide polymorphism. No statistically significant correlation was found between CRC and the 190 G/A CCR2 polymorphism.

Conclusion: The results of this study support the hypothesis that polymorphism in the MCP-1 gene may contribute to the etiology of colorectal cancer.

KEYWORDS:

colorectal cancer, MCP-1, CCR-2, single nucleotide polymorphisms

INTRODUCTION

Inflammation plays an important role in the pathogenesis of colorectal cancer. Among many inflammatory factors that affect cell functioning, the role of receptors that activate signal transduction from the external environment to the cell nucleus is still underestimated. Chemokines play a crucial role in innate and adaptive immunity, and they are involved in many physiological and pathological processes such as cell proliferation, apoptosis, tumor metastasizing, and host defense [1]. Monocyte chemoattractant protein-1 (MCP-1) is a well-known proinflammatory factor. CCR2 (C-C chemokine receptor type 2) is a receptor for MCP-1 as well as for CCL-7 and CCL-13 chemokines. CCR2 transduces signal by increasing intracellular calcium ion concentration. MCP-1 is a chemokine that plays a central role in immunosurveillance in the tumor microenvironment. MCP-1 also controls the recruitment of leukocytes to tissues during inflammation, and performs a number of tumor-promoting activities. Importantly, MCP-1 promotes polarization of macrophages into M2 cells that play immunosuppressive roles and secrete angiogenic factors such as vascular endothelial growth factor [2]. MCP-1 and CCR2 have been linked mostly to chronic inflammatory diseases [3], but also to antitumor immunity [4] and many types of cancer, such as lung cancer [5], prostate cancer, endometrial cancer [6, 7], and breast cancer [8]. These molecules may also be involved in tumor macrophage infiltration [9].

MCP-1 may be associated with cancer pathogenesis; thus, it is important to evaluate whether structural changes in the *MCP-1* and *CCR2* genes can impair their function. Therefore, our goal was to evaluate the role of the -2518 A/G *MCP-1* and 190 G/A *CCR2* single nucleotide polymorphisms (SNP) in colorectal cancer pathogenesis.

MATERIALS AND METHODS

We included 149 patients and 142 healthy blood donors for the -2518 G/A *MCP-1* evaluation, and 214 patients and 144 control subjects for the 190 A/G *CCR2* evaluation (median age of 64 years). The diagnosis of cancer was made after direct colonoscopy and a histopathological examination of biopsies. For staging, the American Joint Committee on Cancer staging classification of histological changes was used. All subjects involved in the study were unrelated Caucasians from the Lodz district, Poland. The study was approved by the local Ethic Committee, and written consent was obtained from each patient or healthy blood donor before study enrollment.

DNA was isolated from peripheral blood using the QIAamp DNA Blood Midi Kit (Qiagen, Chatsworth, CA, USA). Genotyping was performed using restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR). DNA fragments were amplified with the DreamTaq PCR Master Mix (Thermo Scientific, Waltham, MA, USA) according to the manufacturer's instruction, using 250 nM of each primer (Sigma-Aldrich, St. Louis, MO, USA). The primers' sequences are presented in Table 1. The amplified DNA was digested with 5U of an adequate restriction enzyme (New England Biolabs, Ipswich, MA, USA) (Table 1). Restriction fragments were separated on a 3% agarose gel in a TAE buffer. The gel was stained with ethidium bromide and visualized under UV light. More than 10% of the samples were repeated, and the results were 100% concordant.

For statistical analysis, we used the Hardy-Weinberg Equilibrium (HWE) test that was based on the simple chi-squared goodness-of-fit test. The statistics are reported together with corre-

Tab. I. PCR primers and restriction enzymes used

SINGLE NUCLEOTIDE POLYMORPHISM	AMPLICON LENGTH [BP]	PRIMERS SEQUENCES	ANNEALING TEMPERATURE [°C]	RESTRICTION ENZYME
MCP-1 -2518 A/G	930	5'-CCG AGA TGT TCC CAG CAC AG-3' 5'-CTG CTT TGC TTG TGC CTC TT-3'	55	PvuII
CCR-2 190G/A	380	5'-GGA TTG AAC AAG GAC GCA TTT CCC C-3' 5'-TTG CAC ATT GCA TTC CCA AAG ACC C-3'	62	BtsCI

sponding P values for the HWE test. Results were rejected at the significance level $\alpha = 0.05$. Next, to compare the distributions of demographic variables and selected risk factors between patients and controls, the chi-squared test was used. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as measures of the clinical impact. If expected frequencies in 2x2 contingency tables were smaller than 5, the Fisher exact test was used. $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the Statistica software (Statsoft, Tulsa, USA).

RESULTS

The evaluated genotypic frequency distributions conformed to the Hardy-Weinberg Equilibrium expectations. With regard to the -2518 A/G *MCP-1* polymorphism, genotype frequencies were in agreement with the HWE in controls ($\chi^2 = 3.122$; $P = 0.077$) and patients ($\chi^2 = 3.232$; $P = 0.072$). No significant departure from the HWE was found in the genotype distributions of the 190 G/A *CCR2* polymorphism in controls ($\chi^2 = 0.136$; $P = 0.712$) or patients ($\chi^2 = 1.413$; $P = 0.235$).

We analyzed the -2518 A/G *MCP-1* and 190 G/A *CCR2* polymorphic variants in patients with CRC and correlated these findings with different stages of colorectal cancer. There was an increased frequency of the GG genotype in patients with CRC (OR 4.09, 95% CI 1.13-14.86, $p = 0.0221$; Table 2). We also classified patients according to the TMN classification of American Joint Committee of Cancer; there was no correlation between cancer progression and any of the investigated *MCP-1* SNP genotypes (Table 3).

We also analyzed the 190 G/A *CCR2* single nucleotide polymorphism. There was no correlation between the 190G/A *CCR2* polymorphism and colorectal cancer (Table 4). The samples were also classified according to the cancer stage; however, there was no statistically significant relationship between the groups (Table 5). Some analyses could not be performed due to the lack of subjects with specific cancer stages.

DISCUSSION

MCP-1 expression and macrophage infiltration are correlated with poor prognosis and metastatic disease in patients with breast cancer [10]. Recruitment of inflammatory monocytes that express CCR2, as well as subsequent recruitment of metastasis-associated macrophages and their interaction with metastasizing tumor cells is dependent on MCP-1 synthesized by both the tumor and the parenchyma. Inhibition of the MCP-1/CCR2 signaling pathways blocks the recruitment of inflammatory monocytes, thereby inhibiting *in vivo* metastasizing and

Tab. II. Odd ratios (OR) and 95% confidence intervals (95% CI) for the -2518 A/G MCP-1 genotypes investigated in patients with colorectal cancer (CRC) and healthy controls.

MCP-1 GENOTYPE/ ALLELE	CONTROL GROUP [NO OF SUBJECTS]	CRC [NO. OF SUBJECTS]	OR	CI (95%)	P
AA	84	89	ref		
AG	55	47	0,81	0,49-1,32	0,3896
GG	3	13	4,09	1,13-14,86	0,0221
A	223	225	ref		
G	61	73	1,19	0,81-1,75	0,3864

ref – wartość referencyjna

$p < 0,05$ uznano za istotne statystycznie

Tab. IV. Odd ratios (OR) and 95% confidence intervals (95% CI) for the 190 G/A CCR2 genotypes in patients with colorectal cancer (CRC) and healthy controls.

CCR2 GENOTYPE/ ALLELE	CONTROL GROUP [NO OF SUBJECTS]	CRC [NO OF SUBJECTS]	OR	CI (95%)	P
GG	108	157	ref		
GA	34	55	1,11	0,68-1,82	0,6713
AA	2	2	0,69	0,09-4,96	0,5409 F
G	250	369	ref		
A	38	59	1,05	0,68-1,63	0,8231

ref – reference value

$P < 0.05$ was considered statistically significant.

F - Fisher Exact Test

improving survival of tumor-bearing mice [10]. Additionally, the MCP-1/CCR2 signaling axis appears to play a dual role in mediating early tumor immunosurveillance and sustaining the growth and progression of established tumors [11]. Myeloid cells, i.e., the selective CD11b/Gr1(mid) cell subset, promote the development of liver metastases of colorectal cancer [12]. Zhao et al. (2013) reported that inhibition of MCP-1 signaling and absence of its cognate receptor CCR2 reduced CD11b/Gr1(mid) recruitment and decreased tumor burden. Moreover, an increased expression of MCP-1 in tumor cells correlates with enhanced metastasizing, poor prognosis, and recruitment of CCR2+ Ly6Chi monocytes. Tumor-derived MCP-1 activates CCR2+ endothelium and thus increases vascular permeability *in vivo*. CCR2 deficiency prevents colon carcinoma extravasation and metastasizing. Of note, CCR2 expression on radio-resistant cells or endothelial cells restores extravasation and metastasizing in *Ccr2*^{-/-} mice. Reducing CCR2 expression on myeloid cells decreases but does not prevent metastasizing. MCP-1-induced vascular permeability and metastasizing is dependent on JAK2-Stat5 and p38MAPK signaling [13]. Chun et al. (2015) found that MCP-1 promotes colorectal carcinogenesis by influencing MDSC accumulation and func-

Tab. III. Odd ratios (OR) and 95% confidence intervals (95% CI) for the -2518 A/G MCP-1 genotypes in patients with different stages of colorectal cancer (CRC).

MCP-1 GENOTYPE/ ALLELE	STADIUM				II VS I			III VS I			III VS II			IV VS I	IV VS II	IV VS III
	I	II	III	IV	OR	CI	P	OR	CI	P	OR	CI	P	OR	OR	OR
AA	12	32	40	3	ref			ref			ref			ref	ref	ref
AG	7	19	21	0	1,02	0,34–3,03	1	0,9	0,31–2,63	0,8415	0,88	0,41–1,92	0,7518	n/a	n/a	n/a
GG	2	4	7	0	0,75	0,12–4,64	0,5453 F	1,05	0,19–5,74	0,6624 F	1,4	0,38–5,21	0,4344 F	n/a	n/a	n/a
A	31	83	101	6	ref			ref			ref			ref	ref	ref
G	11	27	35	0	0,92	0,41–2,07	0,8415	0,98	0,44–2,15	1	1,07	0,59–1,9	0,8231	n/a	n/a	n/a

ref – reference value

P < 0.05 was considered statistically significant.

F - Fisher Exact Test

Tab. V. Odd ratios (OR) and 95% confidence intervals (95% CI) for the 190 A/G CCR2 genotypes in patients with different stages of colorectal cancer (CRC).

CCR2 GENO- TYPE/ ALLELE	STADIUM				II VS I			III VS I			III VS II			IV VS I			IV VS II			IV VS III			
	I	II	III	IV	OR	CI 95%	P	OR	CI 95%	P	OR	CI 95%	P	OR	CI 95%	P	OR	CI 95%	P	OR	CI 95%	P	
GG	31	57	63	3	ref			ref			ref			ref			ref			ref			
GA	6	19	27	1	1,72	0,62–4,76	0,2921	2,21	0,83–5,92	0,1075	1,29	0,65–2,56	0,4751	1,72	0,15–19,49	0,5421 F	1	0,09–10,2	0,7411 F	0,78	0,08–7,82	0,6565 F	
AA	0	1	1	0	n/a			n/a			0,9	0,06–14,8	0,7269 F	n/a			n/a			n/a			
G	68	133	153	7	ref			ref			ref			ref			ref			ref			
A	6	21	29	1	1,79	0,69–4,64	0,2269	2,09	0,85–5,41	0,1131	1,2	0,65–2,2	0,5541	1,62	0,17–15,45	0,5266 F	0,9	0,11–7,73	0,7027 F	0,75	0,09–6,36	0,3002 F	

ref – reference value

P < 0.05 was considered statistically significant.

F - Fisher Exact Test

tion and by promoting a tumor-permissive tissue microenvironment. MCP-1 levels were increased in patients with colitis-associated colorectal cancer (CRC), adenocarcinomas, and adenomas. Deletion of *MCP-1* blocked progression from dysplasia to adenocarcinoma and reduced the number of colonic MDSCs in a mouse model of spontaneous colitis-associated CRC [14]. Because MCP-1 and CCR2 play an important role in colorectal cancer pathogenesis, we expected that the -2518 A/G *MCP-1* and 190 G/A *CCR2* polymorphisms can be associated with the disease.

Binding of Interferon Regulatory Factor-1 (IRF-1) and/or the Prep1/Pbx 2 transcription factor complex is influenced by the -2518 A/G *MCP-1* polymorphism [15]. It has been shown that the -2518 A/G *MCP-1* single nucleotide polymorphism is correlated with a higher expression of MCP-1 and therefore may affect carcinogenesis [16]. We have reported that GG homozygotes with regard the -2518 A/G *MCP-1* SNP are at a higher risk of colorectal cancer. To date, no other research on the role of this polymorphism in CRC has been published. The association between -2518 A/G *MCP-1* SNP and other cancers is not clear. Sáenz-López et al. (2008) found no overall association between prostate cancer risk and *MCP-1* single nucleotide polymorphisms [17]. In patients with nasopharyngeal carcinoma

after initial radiotherapy, Tse et al. (2007) reported that carriers of the AA and AG genotypes were more likely to have distant metastases than carriers of the GG genotype (hazard ratio 2.21; P = 0.017, and hazard ratio 2.23; P = 0.005, for AA and AG genotype, respectively) [18]. In patients with breast cancer, Ghilardi et al. (2005) found at least one G allele in the metastasis positive (M+) subgroup at the end of the follow-up period; AA vs. AG + GG: OR = 2.83 (95% CI, 1.06-7.64; P = 0.020); M+ vs. M- patients and M+ vs. controls: OR was 2.09 (95% CI, 1.15-7.52; P = 0.012) [19]. On the other hand, there were no statistically significant differences in the -2518 A/G *MCP-1* genotypes between patients with breast tumors and controls in the Polish population [20].

Another investigated polymorphism was the 190 G/A *CCR2* polymorphism. The A G to A transition at position 190 leads to an amino acid change Val64Ile located in the first transmembrane domain of the receptor protein. This change decreases the affinity of MCP-1 to that receptor since the binding of MCP-1 with the CCR2 receptor is mediated by another transmembrane domain. This polymorphism is associated with a delay in disease progression in HIV-1 infected individuals [21]. Valdes et al. (2002) reported that the extent of coronary artery calcification was significantly lower in patients with the *CCR2*-Ile64

variant (AA genotype) [22]. The frequency of homozygotes for the *CCR2*-64Ile was also found to be lower in sarcoidosis and Alzheimer's disease than in controls, indicating that the GG genotype of the 190 G/A *CCR2* SNP could be associated with more pronounced inflammation in autoimmune and/or inflammatory diseases [23, 24]. Moreover, an animal study suggested that IFN- γ -induced MCP-1 expression contributes to myasthenia gravis progression and that *CCR2* is involved in disease progression or disease induction [25, 26]. The *CCR2*-64I variant (AA genotype) was significantly associated with cervical cancer when cases were compared to controls ($P = 0.001$) in an African population, but did not affect the susceptibility to HPV [27]. Previous research also showed that the AA genotype was associated with breast cancer ($p = 0.017$; $df = 2$) [28]. There were no prior reports on the role of the 190 G/A *CCR2* in colorectal cancer, and our report addressed this issue.

CONCLUSIONS

Chemokines are implicated in colorectal cancer pathogenesis and progression due to a potential link between the disease and prolonged inflammation in inflammatory bowel diseases. Our results indicate a potential role of the -2518 A/G *MCP-1* polymorphism in colorectal cancer pathogenesis. We did not find such an association with respect to the 190 G/A *CCR2* SNP. Dysfunction of chemokine pathways caused by single nucleotide polymorphisms, although not essential for survival, could be critical for immunosurveillance and eradication of new cancer cells. Our analysis performed according to cancer stage showed no association with the studied polymorphisms probably due to a small number of subjects. Thus, larger studies are needed. Further research in patients with colorectal cancer and with the use of animal models is necessary to verify our observations.

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