RESEARCH ARTICLE

Association of Adiponectin Receptor (Adipo-R1/-R2) Expression and Colorectal Cancer

Talat Ayyildiz[1]*, Enver Dolar[2], Nesrin Ugras[3], Saduman Balaban Adim[3], Omer Yerci[3]

Abstract

Introduction: Human adiponectin (ApN) is a 30 kDa glycoprotein of 244-amino acids which is extensively produced by adipocytes. ApN acts via two receptors, namely adiponectin receptor-1 (Adipo-R1) and adiponectin receptor-2 (Adipo-R2). Studies have shown the presence of Adipo-R1 and Adipo-R2 expression immunohistochemically in human colorectal cancers (CRCs). However, only a few studies exist which investigated effects of adiponectin receptor expression on CRC characteristics. Objectives: In the present study, we aimed to explore Adipo-R1/-R2 expression in human colorectal cancers and any association with clinicopathological characteristics and survival. Materials and Methods: The study enrolled 58 colorectal cancer patients with tumor resection and a control group of 30 subjects with normal colon mucosa. Results: Positivity for Adipo-R1/-R2 expression was significantly more common in the control group in comparison to the patient group (both p<0.001). There was no significant association between Adipo-R1/-R2 expression and clinicopathological characteristics including age, sex tumor location, pTNM stage, Duke's stage, metastasis, histological differentiation, perineural invasion, venous invasion sex, lymphatic invasion, cancer-related mortality, tumor size and recurrence. Adipo-R1/-R2 positivity was also not significantly linked to progression-free or overall survival [p values (0.871, 0.758) and (0.274, 0.232), respectively]. Conclusions: Although significantly reduced Adipo-R1/-R2 expression was found in colorectal cancer patients, it had no influence on survival.

Keywords: Adiponectin receptor - Adipo-R1/-R2 - colorectal carcinoma - prognosis

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Introduction

Colorectal cancer is the third leading cause of all cancer-related deaths in both males and females (Siegel et al., 2012) and it is still a serious threat to public health due to its morbidity and mortality. Tumor stage as well as predictive and prognostic biomarkers have been reported to be the major prognostic factors in colorectal cancer (Wolpin and Mayer, 2008; Colussi et al., 2013). Thus, for patients with colorectal cancer, it is important to define prognostic factors associated with tumor stage more adequately.

Human adiponectin (ApN) is a 30 kDa glycoprotein of 244-amino acids which is extensively produced by the adipocytes (Goldfine and Kahn, 2003). It has antiatherogenic, antidiabetic and insulin sensitizing properties (Ouchi et al., 1999; Ouchi et al., 2001; Matsuzawa et al., 2003). Reduced ApN levels seem to be associated with development of insulin resistance, diabetes mellitus, metabolic syndrome, hypertension, coronary artery disease, non-alcoholic liver disease (NAFLD) and inflammatory bowel disease (Kadowaki et al., 2002; Kazumi et al., 2002; Kamada et al., 2007; Kojima et al., 2011; Rodrigues et al., 2012). Adiponectin has been shown to demonstrate antitumor activity by suppressing tumor neoangiogenesis (Brakenhielm et al., 2004). In a separate study, it was suggested that adiponectin may reduce the severity of chronic inflammation-induced colorectal carcinoma by preventing goblet cell apoptosis (Saxena et al., 2013). Adiponectin was also suggested to contribute to carcinogenesis in obesity-related cancers due to its effects on insulin resistance and direct action on tumor cells (Kelesidis et al., 2006; Dalamaga et al., 2012; Joshi and Lee, 2014). Reduced circulatory levels of adiponectin have been shown in obese patients and implicated in the development of obesity-related malignancy (Yang et al., 2002; Cnop et al., 2003). Low ApN levels were found in breast, endometrial, prostate, colon and gastric cancers (Mantzoros et al., 2004; Ishikawa et al., 2005; Michalakis et al., 2007; Kumor et al; 2009; Gonullu et al., 2010; Chen et al., 2012; Gulcelik et al., 2012; Ho et al., 2012). A positive correlation was shown between body-mass index and colorectal cancer in several studies (Murphy et al., 2000; Moore et al., 2004). Some authors have reported an inverse relationship between serum ApN and colorectal carcinoma and also between serum ApN and accumulation

*[1]Department of Gastroenterology, Medical Faculty, Ondokuz Mayis University, Samsun, Turkey, [2]Department of Gastroenterology, [3]Department of Pathology, Medical Faculty, Uludag University, Bursa, Turkey *For correspondence: talatayy@gmail.com*

of fat in visceral tissues and adenoma development (Otake et al., 2005; Wei et al., 2005).

On the other hand, some studies showed lack of any association between ApN plasma levels and the development of colorectal cancer and an inverse relationship with ApN levels was reported only for large adenomas (≥5 mm) (Lukanova et al., 2006; Fukumoto et al., 2008). Yamauchi et al. demonstrated that ApN acts via its two receptors, namely Adiponectin receptor-1 (Adipo-R1) and Adiponectin receptor-2 (Adipo-R2) (Yamauchi et al., 2003). In recent studies, the expression of Adipo-R1 and Adipo-R2 was shown immunohistochemically in human colorectal cancers (Williams et al., 2008; Yoneda et al., 2008). Currently, there are a few studies exist which addressed adiponectin receptor expression and its effects in colorectal cancer. In the present study, we examined whether there was an association between Adipo-R1 and Adipo-R2 expression in colorectal tumor tissues and certain clinicopathological characteristics (age, sex, tumor size and location, tumor stage and histological differentiation) and survival using immunohistochemical methods.

Patients and Methods

Study protocol

This study had a retrospective design. Medical files of patients who were followed and treated in our university hospital were reviewed and pathologic specimens of those patients with adequate data were examined. A total of 58 patients (34 males, 24 females) with primary tumor resection who had been classified using TNM staging system were enrolled in the study.

Thirty subjects (21 males, 9 females) who had undergone intestinal resection due to various reasons (eg., trauma, megacolon) without any underlying malignant or inflammatory conditions were enrolled as control group. Local ethics committee approval was obtained for the conduct of the study.

Immunohistochemical staining

The presence of Adipo-R1 and Adipo-R2 expression in formalin fixed paraffin embedded tissues was investigated using immunohistochemical staining. Adipo-R1 and Adipo-R2 (ab126611 and ab77612, respectively; Abcam, Inc., Cambridge, MA, USA; working dilution 1/250) were used as the primary antibodies. Streptavidin-biotin methodology was used for immunohistochemical staining. Tissue sections (Four micrometers thickness) were transferred onto lysine-coated slides and deparaffinized with overnight incubation at 60°C. They were deparaffinized and rehydrated. Then, they were boiled in a microwave oven for 20 minutes at a temperature equivalent to 750 watts. Following incubation with 3% hydrogen peroxide, the sections were kept at protein blocking antibody for 10 minutes and then incubated with the primary antibody for one hour at room temperature. Then, they were incubated with anti-rabbit biotinylated secondary antibody for one hour and streptavidin-HRP for 15 minutes respectively. Subsequently, diaminobenzidine (DAB) chromogen solution was applied for 10 minutes.

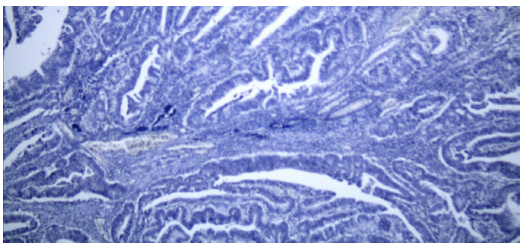

Figure 1. Adipo-R1 Negative -Tumor tissue (DABx400)

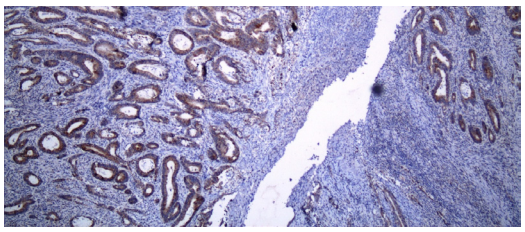

Figure 2. Adipo-R1 Positive - Tumor tissue (DABx400)

After counterstaining with Hematoxylin, the sections were dehydrated and cleared. The sections were examined by two experienced pathologists under a light microscope with respect to the extent and intensity of staining. Sections with significant involvement and extension of 5% or greater were considered positive (Figures 1, 2).

Statistical analysis

Descriptive values of study data were provided as number and percent frequencies and mean±SD in tabulations. Chi-square test was used to compare patient and control groups with respect to age and sex distribution and Adipo-R1 and Adipo-R2 positivity. Additionally, relationships between categorical variables and Adipo-R1 and Adipo-R2 positivity and association between Adipo-R1 and Adipo-R2 were examined using an appropriate chi-square analysis. Mann-Whitney U test was used to compare patients with positive Adipo-R1/Adipo-R2 expression versus those with negative Adipo-R1/-R2 expression in relation to the number of cancerous lymph nodes and total excised lymph nodes. Factors affecting the time to Progression- Free Survival (PFS) and Overall Survival (OS) were analyzed using a Cox regression model. After completion of statistical tests, any results with an associated p value less than or equal to 0.05 were considered statistically significant. A Predictive Analytics Software [SPSS (Statistical Package for the Social Sciences) version18]) package was used for estimations.

Table 1. Descriptive Values for Clinicopathological Characteristics of Control Group and Colorectal Cancer Patients

Characteristics	Category	Control		Patients		P value
		n	(%)	n	(%)	
Age	<55	16	53.3	16	27.6	0.017
	≥55	14	46.7	42	72.4	
Sex	Female	9	30	24	41.4	0.296
	Male	21	70	34	58.6	
Adipo-R1	Absent	2	6.7	30	51.7	<0.001
	Present	28	93.3	28	48.3	
Adipo-R2	Absent	1	3.3	22	37.9	<0.001
	Present	29	96.7	36	62.1	

Table 2. Comparative Results for Colorectal Cancer Patients with Adipo-R1/-R2 Expression Positivity or Negativity in Relation to the Number of Cancerous Lymph Nodes and Total Number of Excised Lymph Nodes

Characteristics	Adipo-R1		P	Adipo-R2		P
	Negative (Mean±SD)	Positive (Mean±SD)		Negative (Mean±SD)	Positive (Mean±SD)	
Cancerous lymph node	4.76±14.35	2.14±2.57	0.614	2.63±4.32	4.02±12.91	0.788
Total number of excised lymph nodes	22.00±10.47	16.75±9.85	0.131	20.27±11.71	18.97±13.46	0.4

Table 3. The Association of Adipo-R1/-R2 Positivity and Clinicopathological Characteristics in Patients with Colorectal Cancer

Characteristics		Adipo-R1					Adipo-R2				
		Negative		Positive		P	Negative		Positivee		P
		n (number)	(%)	n	(%)		n	(%)	n	(%)	
Age	<55	9	28.10%	23	41.10%	0.225	8	34.80%	24	36.90%	0.854
	≥55	23	71.90%	33	58.90%		15	65.20%	41	63.10%	
Sex	Female	14	43.80%	19	33.90%	0.36	9	39.10%	24	36.90%	0.851
	Male	18	56.30%	37	66.10%		14	60.90%	41	63.10%	
Tumor Localisation	Rectum	10	33.30%	12	42.90%	0.774	9	40.90%	13	36.10%	0.378
	Sigmoid colon	9	30.00%	9	32.10%		5	22.70%	13	36.10%	
	Descending colon	1	3.30%	1	3.60%		0	0.00%	2	5.60%	
	Right colon	10	33.30%	6	21.40%		8	36.40%	8	22.20%	
Pathological stage (pTNM)											
	Stage 1+ Stage 2	14	46.70%	11	39.30%	0.571	10	45.50%	15	41.70%	0.777
	Stage 3+ Stage 4	16	53.30%	17	60.70%		12	54.50%	21	58.30%	
T stage	pT1	1	3.30%	0	0.00%	0.421	1	4.50%	0	0.00%	0.373
	pT2	4	13.30%	1	3.60%		3	13.60%	2	5.60%	
	pT3	24	80.00%	26	92.90%		17	77.30%	33	91.70%	
	pT4	1	3.30%	1	3.60%		1	4.50%	1	2.80%	
N stage	N0	14	46.70%	10	35.70%	0.397	10	45.50%	14	38.90%	0.622
	N1+N2	16	53.30%	18	64.30%		12	54.50%	22	61.10%	
Metastasis (M) stage	M0	26	86.70%	24	85.70%	0.916	19	86.40%	31	86.10%	0.978
	M1	4	13.30%	4	14.30%		3	13.60%	5	13.90%	
Duke's classification	A+B	14	46.70%	11	39.30%	0.571	10	45.50%	15	41.70%	0.777
	C+D	16	53.30%	17	60.70%		12	54.50%	21	58.30%	
Histological Differentiation	Well	8	26.70%	6	21.40%	0.641	4	18.20%	10	27.80%	0.407
	Moderate+ Poor	22	73.30%	22	78.60%		18	81.80%	26	72.20%	
Perineural invasion	Absent	23	76.70%	22	78.60%	0.862	16	72.70%	29	80.60%	0.488
	Present	7	23.30%	6	21.40%		6	27.30%	7	19.40%	
Venous invasion	Absent	27	90.00%	25	89.30%	0.929	20	90.90%	32	88.90%	0.806
	Present	3	10.00%	3	10.70%		2	9.10%	4	11.10%	
Lymphatic invasion	Absent	21	70.00%	18	64.30%	0.643	16	72.70%	23	63.90%	0.406
	Present	9	30.00%	10	35.70%		6	27.30%	13	36.10%	
Cancer related death	Absent	22	73.30%	10	35.70%	0.641	18	81.80%	26	72.20%	0.407
	Present	8	26.70%	6	21.40%		4	18.20%	10	27.80%	
Tumor size	<5 cm	17	56.70%	17	60.70%	0.754	13	59.10%	21	58.30%	0.955
	≥5 cm	13	43.30%	11	39.30%		9	40.90%	15	41.70%	
Recurrence	Absent	24	80.00%	20	71.40%	0.746	18	81.80%	26	72.20%	0.47
	Present	6	20.00%	8	28.60%		4	18.20%	10	27.80%	

Results

The study enrolled a total of 88 subjects including 58 in the patient group (24 females, 34 males; mean age, 60.07±11.40 years) and 30 in the control group (9 females, 21 males; mean age 50.90±18.29 years). Table 1 shows comparative results of patient and control groups in relation to age, sex and Adipo-R1 and Adipo-R2 expression. The percentage of patients over 55 years of age was significantly high ($p<0.017$). However, control group showed a significantly greater rate of positivity for Adipo-R1 and Adipo-R2 expression in comparison to patient group (both $p<0.001$). It is clear from the table that there is a significant relationship between Adipo-R1 positivity and Adipo-R2 positivity in both patients and control subjects. Comparison of the numbers of cancerous lymph nodes and total excised lymph nodes in relation to Adipo-R1 and Adipo-R2 expression did not yield a significant association (Table 2).

Table 3 shows the breakdown of clinicopathological characteristics of patients with positive or negative Adipo-R1/-R2 expression. As the table indicates, there is a lack of significant association between Adipo-R1 or Adipo-R2 positivity and patient clinicopathological characteristics including age, sex, tumor location, pTNM stage, Duke's stage, metastasis, histological differentiation, perineural invasion, venous invasion, lymphatic invasion, cancer-related mortality, tumor size and recurrence.

Those clinicopathological characteristics having a significant effect on time to progression-free survival and overall survival of patients were also examined (Table 4). It was clearly observed that both time to progression-free survival and time to overall survival were significantly associated with a more advanced histopathological pTNM stage (3+4), Duke's stage (C+D) or pN stage (N1+N2), the presence of metastasis, perineural invasion and venous invasion, recurrence and greater number of cancerous lymph nodes. Tumor size was significantly associated

Table 4. The Association of Adipo-R1/-R2 Expression and Clinicopathological Characteristics with Progression-Free Survival and Overall Survival in Patients with Colorectal Cancer

Characteristics		Progresses free survival		Overall survival	
		HR * (95% CI)	P value	HR* (95% CI)	P value
Age	<55		Reference category		
	≥55	2.847 (0.626-12.952)	0.176	2.927 (0.651-13.172)	0.162
Sex	Female		Reference category		
	Male	2.279 (0.712-7.292)	0.165	2.322 (0.724-7.449)	0.156
Adipo-R1	Negative		Reference category		
	Positive	1.092 (0.376-3.173)	0.871	1.183 (0.406-3.449)	0.758
Adipo-R2	Negative		Reference category		
	Positive	1.911 (0.598-6.108)	0.274	2.03 (0.635-6.490)	0.232
Tumor Localisation	Rectum		Reference category		
	Sigmoid colon	1.158 (0.352-3.817)	0.809	1.227 (0.372-4.050)	0.737
	Descending colon	2.133 (0.248-18.341)	0.49	2.206 (0.256-18.983)	0.471
	Right colon	0.424 (0.082-2.194)	0.306	0.456 (0.088-2.358)	0.349
Pathological stage (TNM)	Stage 1+ Stage 2		Reference category		
	Stage 3+ Stage 4	11 (1.438-84.2)	0.021	10.042 (1.313-76.802)	0.026
N stage	N0		Reference category		
	N1+N2	4.623 (1.03-20.68)	0.045	4.255 (1.952-19.023)	0.043
Metastasis (M) stage	M0		Reference category		
	M1	12.844 (3.844-42.911)	<0.0001	8.936 (2.895-27.583)	<0.0001
Duke's classification	A+B		Reference category		
	C+D	11.004 (1.438-84.2)	0.021	10.042 (1.313-76.802)	0.026
Differentiation	Well		Reference category		
	Moderate+ Poor	1.138 (0.317-4.093)	0.843	1.075 (1.300-3.856)	0.912
Perineural invasion	Absent		Reference category		
	Present	2.911 (1.00-8.784)	0.05	2.711 (1.898-8.184)	0.045
Venous invasion	Absent		Reference category		
	Present	4.029 (1.261-12.87)	0.019	3.576 (1.119-11.430)	0.032
Lymphatic invasion	Absent		Reference category		
	Present	0.689 (0.214-2.224)	0.534	0.668 (1.207-2.148)	0.498
Tumor size	<5 cm		Reference category		
	≥5 cm	0.374 (0.104-1.343)	0.131	4.623 (1.03- 20.68)	0.045
Recurrence	Absent		Reference category		
	Present	7.437 (2.527-21.885)	<0.0001	6.257 (2.141-18.281)	0.001
Cancerous lymph node		1.057 (1.020-1.095)	0.002	1.056 (1.019-1.094)	0.003
Total number of excised lymph nodes		0.978 (0.929-1.030)	0.402	0.977 (0.928-1.029)	0.385

with only overall survival (p=0.045). Contrastingly, neither Adipo-R1/Adipo-R2 expression nor other clinicopathological characteristics such as age, sex, tumor location, histological differentiation, lymphatic invasion, the total number of excised lymph nodes showed a statistically significant association with PFS and OS. The effects of Adipo-R1 and Adipo-R2 expression on overall survival are also indicated.

Discussion

There are a limited number of studies on the association between adiponectin and colorectal carcinoma. In a prospective case-control study, Wei et al. showed a greater risk of colorectal cancer among patients with low plasma adiponectin levels (Wei et al., 2005). However, Lukanova et al. did not identify any relationship between plasma adiponectin levels and CRC (Lukanova et al., 2006). Also, Yoneda et al. showed that there was not any difference between normal colon epithelium and colorectal cancer tissues in Adipo-R1 or Adipo-R2 expression (Yoneda et al., 2008)

We designed this study to elucidate whether there is a relationship between Adipo-R1/R2 expression and

clinicopathological characteristics in colorectal cancer patients mainly because of the contradictory findings which were reported by previous studies that explored the association of adiponectin with CRC. In our study, control group with normal colon epithelium was found to have increased expression of both Adipo-R1 and Adipo-R2 in comparison to patient group with colorectal cancer tissue (both $p<0.001$), suggesting that the risk of colorectal cancer is likely to be increased with lower Adipo-R1/-R2 expression. The fact that a greater number of patients enrolled in our study compared to that of Yoneda et al.'s study may have contributed to obtaining differential results with statistical significance in the present study. In a study on adiponectin expression conducted by Barresi et al. in colorectal cancer patients, while no expression was observed in normal tissue, CRC tissues and particularly high-grade histologically differentiated tumors showed a significant ApN expression (Barresi et al., 2009)

Another remarkable finding of our study was the demonstration of Adipo-R1/-R2 expression both in normal tissue and CRC tissue. We know that adiponectin acts via Adipo-R1/-R2 receptors and thus, based on our findings, we may suggest that adiponectin might have a protective effect against colorectal cancer. Additionally, a linear relationship was observed between Adipo-R1 expression and Adipo-R2 expression in both normal tissue and CRC tissue.

We did not identify a significant relationship between Adipo-R1/-R2 expression and progression-free survival and overall survival. However, some of the clinicopathological characteristics including pTNM stage, Duke's stage, N stage, perineural invasion, venous invasion, recurrence and the total number of excised lymph nodes showed a significant association with survival (PFS and OS). We have seen contradictory results obtained in previous studies on the association of gastric cancer and Adipo-R1/-R2 expression in relation to survival. While Barresi et al. reported a significant association of Adipo-R1/-R2 expression with overall survival, Ayyildiz et al. suggested that there is not any such association (Barresi et al., 2009b; Ayyildiz et al., 2014). In the present study, we did not observe a significant relationship between survival and Adipo-R1/-R2 expression in CRC. As with gastric cancer, large scale studies are needed for CRC.

Sugiyama et al. investigated the effects of globular adiponectin (g-adiponectin) on the cell growth and activation of intracellular signaling pathway in CRC cell lines taking into account the ability of g-adiponectin to bind to both Adipo-R1 and Adipo-R2 receptors (Sugiyama et al., 2009). As a result, they demonstrated that g-adiponectin activated adenosine monophosphate-activated protein kinase (AMPK) and subsequently suppressed mammalian target of rapamycin (mTOR) pathways. Thus, they suggested that adiponectin inhibits colorectal cancer cell growth via activation of AMPK, thereby down-regulating the mTOR pathway. It is known that mTOR plays a key role in cell proliferation, growth, differentiation, migration and viability and aberrant mTOR regulation is present in tumors (Philp et al., 2001; Dancey 2002; Huang and Houghton 2003; Oldham and Hafen 2003; Vogt 2013).

Byeon et al. detected Adipo-R1 and Adipo-R2 in 72% and 68% of human colorectal cancer tissue respectively, by immunohistochemical staining and reported that Adipo-R1 and Adipo-R2 expression levels were inversely related to T stage. They also detected lower Adipo-R1 and Adipo-R2 expression in poorly differentiated adenocarcinoma (Byeon et al., 2010). The corresponding figures in the present study for Adipo-R1/-R2 expression in CRC tissue (51.7% and 37.9%, respectively) were lower than those reported by Byeon et al. Another dissimilar finding was that we did not find a significant association between Adipo-R1/-R2 expression and T stage or histological differentiation.

There are some limitations of our study. It would be better if we could enroll a greater number of patients. Due to the small sample size, we had to combine some of the groups when examining T stage, N stage, TNM stage and histological differentiation in order to conduct meaningful statistical analyses. In addition, the absence of body mass index values of subjects impeded our ability to comment on any association with obesity.

Despite all of these limitations, for the first time ever, increased Adipo-R1/-R2 expression was found in a control group versus CRC patients and we believe that this is an important finding. Further studies would hopefully better establish the role of adiponectin and its receptors in CRC.

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