RESEARCH ARTICLE

Adipo-R1 and Adipo-R2 Expression in Colorectal Adenomas and Carcinomas

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Abstract

Background: Human adiponectin (ApN), a 30 kDa glycoprotein of 244-amino acids which is predominantly produced by adipocytes, exerts its effects via two receptors, namely adiponectin receptor-1 (adipo-R1) and adiponectin receptor-2 (adipo-R2) with differential binding affinity to globular adiponectin. Adiponectin receptor expression has been studied in several cancer tissues. However, there are no studies of colorectal adenomas which are considered to be precursors for colorectal carcinoma (CRC). Objectives: In the present study, the expression of adipo-R1 and adipo-R2 was investigated immunohistochemically in colorectal adenomas and colorectal carcinoma tissues in an attempt to determine associations with these tumors. Materials and Methods: The study enrolled 50 CRC patients with tumor resection and 82 patients who were diagnosed with adenomatous polyps, classified as negative for neoplasia, low-grade dysplasia (L-GD) or high- grade dysplasia (H-GD). Results: Expression of both adipo-R1 and adipo-R2 was found to be significantly lower in the CRCs than in colorectal adenomas (tubular and tubulovillous, p=0.009 and p<0.001, respectively). Adipo-R1 and adipo-R2 expression was also significantly lower in the CRC group when compared with the groups of patients with low grade dysplasia, high-grade dysplasia or no neoplasia (p=0.012 and p<0.001, respectively). In addition, it was observed that adipo-R2 expression was generally positive in the non-neoplastic group irrespective of the adipo-R2 expression. In the L-GD, H-GD and CRC groups, the adipo-R2 result was positive whenever adipo-R1 result was positive but some patients with negative adipo-R1 had positive adipo-R2 (p<0.001, p=0.004, p<0.001, respectively). Conclusions: This study indicated that ApN may play a role in the progression of colorectal adenomatous polyps to carcinoma through actions on adipo-R1 and adipo-R2 receptors.

Keywords: Adiponectin - adipoR1 - adipoR2 - colorectal carcinoma - polyps - progression

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Introduction

Colorectal cancer is the third most prevalent cancer and third leading cause of all cancer-related deaths in both males and females (Siegel et al., 2014).

It is known that colorectal adenomas are among the factors that confer predisposition to CRC development. Current evidence indicates that CRC mostly evolves from preexisting adenomas. Adenomas grow, progressively dedifferentiate and become initially dysplastic and eventually malignant. Increased adenoma size, predominance of villous architecture, and a greater degree of nuclear atypia lead to dysplasia and in situ or invasive carcinoma (Bresalier, 2010). The progression of adenomas into carcinoma via this cascade of events necessitates elucidation of the association between adenomas and cytokines which have been implicated in cancer formation. Adiponectin is a cytokine that has been investigated for its possible association with CRC. Human adiponectin (ApN) is a 30 kDa glycoprotein of 244-amino acids which is predominantly produced by the adipocytes (Goldfine and Kahn, 2003)

ApN has insulin-sensitizing properties and was suggested to show antiatherogenic and antidiabetic properties through inflammatory stimuli-induced NF-kappaB activation (Ouchi et al., 1999; Ouchi et al., 2000; Ouchi et al., 2001; Matsuzawa et al., 2003)

Research has demonstrated that ApN has both negative and positive effects on tumor growth (Hebbard and Ranscht, 2013). Additionally, it was suggested that adiponectin might show antitumor activity by inhibiting tumor angiogenesis and preventing goblet cell apoptosis (Brakenhielm et al., 2004; Saxena et al., 2013).

Reduced circulating levels of adiponectin have been shown in obese patients and implicated in the development of obesity-related malignancies (Cnop et al., 2003;

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Dalamaga et al., 2012; Gulcelik et al., 2012; Joshi et al., 2014). Vascular endothelial growth factor and IL-6 are highly expressed by visceral fat tissue and contribute to cancer development (Lysaght et al., 2011). It has been shown that adiponectin inhibits CRC cell growth by activating adenosine monophosphate-activated protein kinase (AMPK) and suppressing the mammalian target-of-rapamycin (mTOR) pathways (Sugiyama et al., 2009). In a separate study, adiponectin showed anti-cancerogenic activity and prevented growth of colon cancer cells by stimulating AMPK activity *in vitro* (Kim et al., 2010).

Wei et al. reported an inverse relationship between serum ApN and CRC in male subjects (Wei et al., 2005). On the other hand, Otake et al. (2005) have shown that plasma ApN concentration was markedly reduced in colorectal adenoma patients with greater visceral fat area. In the same study, visceral fat area and adiponectin have been associated with the number, size and histology of adenomas (tubular and tubulovillous/villous). Recent studies focusing on colorectal cancer screening have underscored the importance of obesity and increased body mass index (BMI) as risk factors for development of colonic polyps (Zauber et al., 2012).

On the other hand, there are some studies which suggested that plasma ApN levels are not linked with the development of CRC in the long-term (Lukanova et al., 2006).Similarly, several adenoma studies have shown lack of any association between circulating ApN levels and colorectal adenomas (Fukumoto et al., 2008; Danese et al., 2013). ApN acts via adiponectin receptors. Two distinct receptors have been identified with different binding affinity to globular adiponectin, namely adiponectin receptor-1 (Adipo-R1) and adiponectin receptor-2 (Adipo-R2) (Yamauchi et al., 2003; Yamauchi et al., 2014). Many previous studies have reported discordant results on Adipo-R1/Adipo-R2 expression in colorectal cancer (Williams et al., 2008; Yoneda et al., 2008; Ayyildiz et al., 2014a).

No studies are available in literature that examined Adipo-R1/Adipo-R2 expression immunohistochemically in colorectal adenomas. Since adenomatous polyps are a predisposing factor for CRC, there is a need to evaluate their association with Adipo-R1/ Adipo-R2 expression.

In the present study, we investigated Adipo-R1/ Adipo-R2 expression immunohistochemically in cases of colorectal adenoma (a predisposing factor for CRC development) and surgically resected colorectal carcinoma in order to determine whether there is a link between Adipo-R1/Adipo-R2 expression and these tumors. Additionally, neoplastic status (negative for neoplasia, low-grade dysplasia ve high-grade dysplasia) of colorectal adenomas and various other factors such as, age and gender were also included in the analysis.

Materials and Methods

Study Protocol

This study had a retrospective design. Medical files of patients who were followed and treated in Uludag University Hospital were reviewed and pathologic specimens of those patients with adequate data were examined.The study enrolled 50 colorectal cancer patients (20 females, 30 males) and 82 patients diagnosed with adenomatous polyps (34 females, 48 males) which summed to a total of 132 subjects (54 (40.9%) females, 78 (59.1%) males). Colorectal cancer cases were selected from patients who underwent surgical resection and cases of adenomatous polpys were identified in other patients who had polypectomy.

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 -thick were transferred onto lysinecoated 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 15 minutes and streptavidin-HRP for 15 minutes respectively. Subsequently, diaminobenzidine (DAB) chromogen solution was applied for 10 minutes. 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 and 2).

Statistical analysis

Descriptive values of study data are provided as number and percent frequencies and mean±standard deviation (SD) in tabulations and charts. Chi-square test was used to compare study groups with respect to age and gender distribution and Adipo-R1 and Adipo-R2 positivity. Additionally, associations between adenomatous polyps (tubular and tubulovillous) and neoplasia status as determined by histopathological examination (negative for neoplasia, low-grade dysplasia or high-grade dysplasia) were examined using an appropriate chi-square analysis. After completion of statistical tests, any study 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.

Results

The numbers of poor, mild and well tumor differentiation of the patients with colorectal carcinomas

were 13 (26%), 36 (72%) and 1 (2%), respectively. pTNM stage 1, 2,3 and 4 numbers were also 2 (4%), 18 (36%), 23 (46%) and 7 (14%), respectively.

Patients with adenomatous polyps were divided into three histological subgroups including negative for neoplasia, low-grade and high-grade dysplasia and compared with colorectal carcinoma patients with respect to Adipo-R1/Adipo-R2 expression, and sex and age distribution (Table 1) As seen in Table 1, Adipo-R1 positivity was significantly lower in CRC group (p=0.012). Similarly, Adipo-R2 positivity was also significantly lower in CRC group compared to other subgroups (p<0.001). Apart from these findings, sex and age distribution of subgroups were statistically similar.

In addition, patients were divided into 2 groups including those with adenomatous polyps and those with colorectal carcinoma and compared with respect to Adipo-R1 and Adipo-R2 expression (Table 1). As a result, Adipo-R1 and Adipo-R2 positivity rate among CRC patients was found to be significantly lower compared to that of patients with adenomatous polyps.

Excluding carcinoma group, patients without neoplasia were gathered in one group and those with low-grade and high-grade dysplasia in a second group in order to

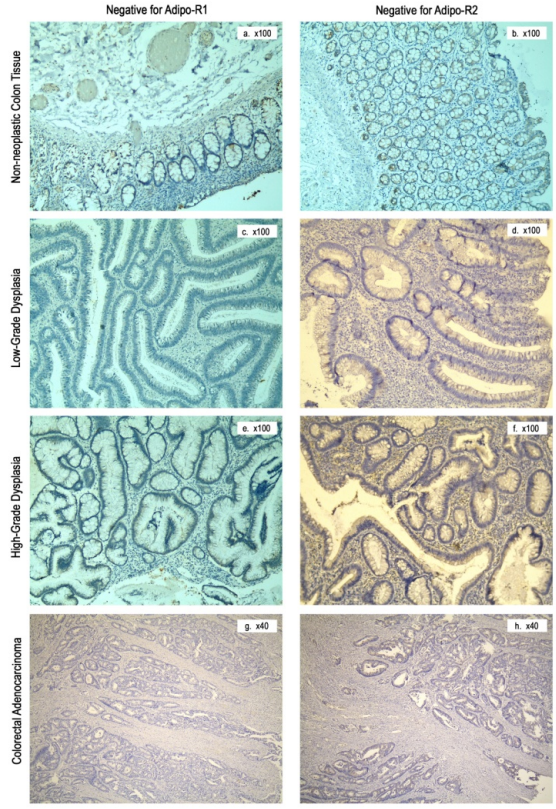

Figure 1. Negative Adipo-R1/-R2 Expression in the Non-neoplasticTissue, Low-Grade Dysplasia, High-Grade Dysplasia and Colorectal Carcinoma

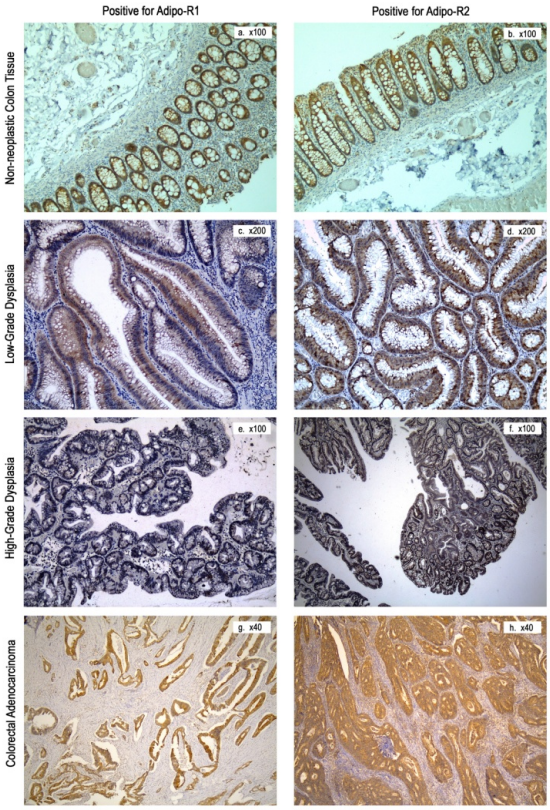

Figure 2. Positive Adipo-R1/-R2 Expression in the Non-neoplastic tissue, Low-Grade Dysplasia, High-Grade Dysplasia and Colorectal Carcinoma.

Table 1. Results of Comparisons between Patients with Colonic Adenomatous Polyps and Colorectal Cancer Patients with Respect to Adipo-R1, Adipo-R2, Age and Sex

Characteristics	Negative for Neoplasia		Low-Grade Dysplasia		High-Grade Dysplasia		Colorectal Carcinoma			Colorectal Polyp		Colorectal Carcinoma		
Category	n	(%)	n	(%)	n	(%)	n	(%)	P value	n	(%)	n	(%)	P value
Adipo-R1														
Negative	15	51.7	7	28	8	28.6	30	60	0.012	30	36.6	30	60	0.009
Positive	14	48.3[ab]	18	72.0b	20	71.4[b]	20	40.0[a]		52	63.4	20	40	
Adipo-R2														
Negative	1	3.4	4	16	3	10.7	22	44	<0.001	8	9.8	22	44	<0.001
Positive	28	96.6[a]	21	84.0[a]	25	89.3a	28	56.0[b]		74	90.2	28	56	
Sex														
Female	17	58.6	9	36	8	28.6	20	40	0.122	34	41.5	20	40	0.868
Male	12	41.4	16	64	20	71.4	30	60		48	58.5	30	60	
Age														
<55	5	17.2	3	12	6	21.4	12	24	0.640	14	17.1	12	24	0.332
≥55	24	82.8	22	88	22	78.6	38	76		68	82.9	38	76	

*Completely different letters located in different columns but in the same row, were shown as statistically significant results

Table 2. Results of Comparison of Patients with Adenomatous Polyps Versus Colorectal Carcinoma Patients with Respect to Adipo-R1 and Adipo-R2 Expressions by Neoplasia Grade for Each Group Separately

	Negative for Neoplasia Adipo-R2		Low-Grade Dysplasia Adipo-R2		High- Grade Dysplasia Adipo-R2		Colorectal Carcinoma Adipo-R2	
	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
Adipo-R1								
Negative	1	14	4	3	3	5	21	9
Positive	0	14	0	18	0	20	1	19
P value		0.326		<0.001		0.004		<0.001

determine an association with Adipo-R1/-R2 expression. It was seen that Adipo-R1 negativity rate was significantly lower in patients with neoplasia compared to those without any neoplasia (p=0.035).

Negativity and positivity rates of adipo-R2 expression did not significantly differ between these groups (p=0.150). In other words, although negativity rate was higher in patients with neoplasia (13.2%) in comparison to those without neoplasia (3.4%), the difference was not statistically significant.

Histopathological examination findings of subjects diagnosed with adenomatous polyps (tubular and tubulovillous adenomas) are shown that examination findings were similar for subgroups of non-neoplastic, low-grade and high-grade neoplasia (p=0.841).

Lastly, positivity for Adipo-R1/Adipo-R2 expression and its association with each group were assessed separately (Table 2). Table shows that irrespective of the Adipo-R1 result, Adipo-R2 result was generally positive only for non-neoplastic group (p=0.326). In addition, for the group with neoplasia, when Adipo-R1 was positive Adipo-R2 positivity was observed but when Adipo-R1 was negative, half of Adipo-R2 results were negative and other half were positive.

As the table indicates, about one third of patients with neoplasia (L-GD ve H-GD) had negative Adipo-R1 results. Adipo-R2 results were examined for those with negative Adipo-R1 results and nearly half of these patients were found to have negative Adipo-R2 results and the other half exhibited positive Adipo-R2 results. However, almost two-thirds of patients with neoplasia had positive Adipo-R1 results and all of their Adipo-R2 results were positive. Based on these findings, we might assume that, for patients with neoplasia, Adipo-R2 results would also be positive when Adipo-R1 results are positive but there will be 50:50 chance of seeing negative Adipo-R2 results when Adipo-R1 is negative.

However, for patients with colorectal carcinoma, positive Adipo- R2 results would be observed when Adipo-R1 results are positive but the majority of Adipo-R2 results would be negative and only a portion would be positive when Adipo-R1 is negative.

Discussion

Obesity and associated disorders increase the risk for development of a variety of gastrointestinal cancers. The underlying mechanism is unclear; however, chronic inflammation associated with obesity has been implicated in the process. Innate immunity, cytokines such as adiponectin and leptin, insulin-like growth factors, gut microbiota and several other factors may also be involved (Tilg and Moschen, 2014).

Clinical correlation studies have shown that lower levels of serum APN are associated with increased malignancy of various cancers. However, there are fewer studies on Adipo-R1/ Adipo-R2 expression in cancers compared to serum adiponectin-based studies. We see inconsistent results reported by previous studies examining Adipo-R1/Adipo-R2 expression in gastrointestinal tumors. While Barresi et al. reported a significant association of Adipo-R1/ Adipo-R2 expression and overall survival in gastric tumors, others suggested that there is not any such relation (Barresi et al., 2009a; Ayyildiz et al., 2014b). Few studies exist in literature on Adipo-R1/Adipo-R2 expression in patients with colorectal cancer. One study reported that there was no difference between normal colon epithelium and colorectal cancer tissues in Adipo-R1 and Adipo-R2 expression (Yoneda et al., 2008).

Canhoroz et al. have shown that adinopectin expression was not associated with overall survival in patients with stage 2 and 3 (TNM stage) colorectal carcinoma (Canhoroz et al., 2014). Barresi et al. (2009a) reported that adiponectin expression does not occur in colorectal cancer patients but they observed a significant level of ApN expression in CRC tissues and particularly in histologically differentiated high-grade tumors (Barresi et al., 2009b). Contrastingly, Ayyildiz et al. found adiponectin receptor expression both in normal colon tissue and colon cancer tissue. Moreover, they reported significantly increased Adipo-R1/ Adipo-R2 expression in normal colon epithelium versus colorectal cancer tissue (Ayyildiz et al., 2014a).

There are no studies in literature on Adipo-R1/ Adipo-R2 expression in colorectal adenomas. However, some studies exist which have established a link between serum adiponectin levels and colorectal adenomas. Danese et al. reported no association between plasma adiponectin level and development of colorectal adenoma (Danese et al., 2013). In a separate study, colorectal adenomas have not been associated with anthropometric measures and adiposity-related laboratory variables such as parameters of insulin resistance and serum adiponectin level (Chronis et al., 2011). Also, Bobe et al. (2010) explored the relationship between serum levels of adiponectin and adenoma recurrence and did not find a significant association.

In the current study, patients with adenomatous polyps (tubular and tubulovillous) were divided into three histological subgroups including negative for neoplasia,

low-grade and high-grade dysplasia and compared with colorectal carcinoma patients with respect to Adipo-R1/Adipo-R2 expression. Adipo-R1/Adipo-R2 expression was significantly lower in CRC group. Similar results were obtained when adenomatous polyps were analyzed in aggregate within CRC patients and again, significantly low Adipo-R1/Adipo-R2 expression was observed. These results correlate with those of other studies (Fukumoto et al., 2008; Bobe et al., 2010; Chronis et al., 2011; Danese et al., 2013) which examined the association between serum adiponectin levels and colorectal adenomas. However, consistent with Ayyildiz et al.'s study, we observed a low level of ApN receptor expression in CRC patients (Ayyildiz et al., 2014a).

Adiponectin exerts its effect via Adipo-R1 and Adipo-R2. Considering the cascade of events that leads to progression of adenoma to colon cancer, one might expect to see decreased Adipo-R1 and Adipo-R2 expression with higher grade of neoplasia. When we reviewed our results in that context, Adipo-R1 expression was found to be significantly low in the groups with neoplasia (L-GD and H-GD) versus non-neoplastic group; Adipo-R2 expression was also reduced but not at a statistically significant level. This suggests that Adipo-R1 and Adipo-R2 expressions are correlated with transformation of adenomatous polyps to malignancies.

A noteworthy result of our study was the occurrence of Adipo-R2 expression in non-neoplastic group irrespective of Adipo-R1 expression, a finding which was not observed in patients with low-grade and high-grade dysplasia or CRC group. However, only about half of the patients in other groups showed Adipo-R2 expression when Adipo-R1 expression was absent, suggesting that there is a significant association between Adipo-R1 negativity and Adipo-R2 positivity during the malignant process. However, Adipo-R2 expression is present almost always when Adipo-R1 is expressed in dysplastic and CRC groups.

Our study has some limitations. Anthropometric measures, body mass index and dietary habits were not available for patients with adenoma. There were a small number of patients diagnosed as having only villous adenoma which precluded their inclusion in the study. We could have identified those colorectal cancer patients with concomitant adenomatous polyps if they had any, and inclusion of such tumors would have made a different contribution to our study.

In conclusion, a significantly low level of Adipo-R1/Adipo-R2 expression was found in colorectal cancer patients compared to those with colorectal adenomatous polyps in the present study. This finding strengthens the hypothesis that adiponectin may be involved in CRC pathogenesis via its receptors (Bobe et al., 2010).

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