Adiponectin Receptor (Adipo-R1/-R2) Expression in Colorectal Cancer

Talat Ayyildiz¹*, Enver Dolar², Nesrin Ugras³, Saduman Balaban Adim³, Omer Yerci³

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

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, anti diabetic 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...
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 700 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.

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 n (%) | Patients n (%) | P value |
|-----------------|----------|---------------|---------------|---------|
| 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)     |         |
Asian Pacific Journal of Cancer Prevention, Vol 15, 2014

DOI:http://dx.doi.org/10.7314/APJCP.2014.15.21.9385

Adiponectin Receptor (Adipo-R1/R2) Expression in Colorectal Cancer

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 (Negative n (Mean±SD)) | P | Adipo-R2 (Negative n (Mean±SD)) | P |
|-----------------|---------------------------------|---|---------------------------------|---|
| 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 Positive n (%) | P | Adipo-R2 Positive n (%) | P |
|-----------------|-------------------------|---|-------------------------|---|
| Age <55 | 28.10% 23 | 41.10% 0.225 | 34.80% 24 | 36.90% 0.854 |
| ≥55 | 71.90% 33 | 58.90% 15 | 65.20% 41 | 63.10% |
| Sex | Female 43.80% 19 | 33.90% 0.36 | 39.10% 24 | 36.90% 0.851 |
| Male | 56.20% 18 | 66.10% 14 | 60.90% 41 | 63.10% |
| Tumor Localisation | Rectum 33.30% 10 | 42.90% 0.774 | 40.90% 13 | 36.10% 0.378 |
| Sigmoid colon | 30.00% 9 | 32.10% 5 | 22.70% 13 | 36.10% |
| Descending colon | 3.00% 1 | 3.60% 0 | 0.00% 2 | 5.60% |
| Right colon | 33.30% 10 | 21.40% 8 | 36.40% 8 | 22.20% |
| Pathological stage (pTNM) | Stage 1+ Stage 2 46.70% 14 | 39.30% 0.571 | 45.50% 10 | 41.70% 0.777 |
| Stage 3+ Stage 4 | 53.30% 16 | 60.70% 12 | 54.50% 21 | 58.30% |
| T stage | pT1 3.30% 1 | 0.00% 0.421 | 4.50% 1 | 0.00% 0.373 |
| pT2 | 13.30% 4 | 3.60% 3 | 13.60% 2 | 5.60% |
| pT3 | 80.00% 24 | 92.90% 17 | 77.30% 33 | 91.70% |
| pT4 | 3.30% 1 | 3.60% 1 | 4.50% 1 | 2.80% |
| N stage | N0 46.70% 14 | 35.70% 0.397 | 45.50% 10 | 38.90% 0.622 |
| N1+N2 | 53.30% 16 | 64.30% 12 | 54.50% 22 | 61.00% 0.978 |
| Metastasis (M) stage | M0 86.70% 26 | 85.70% 0.916 | 86.40% 19 | 86.10% 0.978 |
| M1 | 13.30% 4 | 14.30% 3 | 13.60% 5 | 13.90% |
| Duke’s classification | A+B 46.70% 14 | 39.30% 0.571 | 45.50% 10 | 41.70% 0.777 |
| C+D | 53.30% 16 | 60.70% 12 | 54.50% 21 | 58.30% |
| Histological Differentiation | Well 26.70% 8 | 21.40% 0.641 | 18.20% 4 | 27.80% 0.407 |
| Moderate+ Poor | 73.30% 22 | 78.60% 18 | 81.80% 26 | 72.20% |
| Perineural invasion | Absent 76.70% 23 | 78.60% 0.862 | 72.70% 16 | 80.60% 0.488 |
| Present | 23.30% 7 | 21.40% 6 | 27.30% 6 | 19.40% |
| Venous invasion | Absent 90.00% 27 | 89.30% 0.929 | 90.90% 20 | 88.90% 0.806 |
| Present | 10.00% 3 | 10.70% 2 | 9.10% 4 | 11.10% |
| Lymphatic invasion | Absent 70.00% 21 | 64.30% 0.643 | 72.70% 16 | 63.90% 0.406 |
| Present | 30.00% 9 | 35.70% 6 | 27.30% 7 | 36.10% 0.407 |
| Cancer related death | Absent 73.30% 22 | 73.30% 0.641 | 81.80% 18 | 72.20% 0.407 |
| Present | 26.70% 8 | 21.40% 4 | 18.20% 10 | 27.80% |
| Tumor size | <5 cm 56.70% 17 | 60.70% 0.754 | 59.10% 13 | 58.30% 0.955 |
| ≥5 cm | 43.30% 13 | 39.30% 9 | 40.90% 15 | 41.70% |
| Recurrence | Absent 80.00% 24 | 71.40% 0.746 | 81.80% 18 | 72.20% 0.47 |
| Present | 20.00% 6 | 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...
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.

**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                        | Progression-free survival | Overall survival |
|----------------------------------------|---------------------------|------------------|
|                                        | HR* (95% CI)              | P value          | HR* (95% CI)    | P value          |
| Age                                    |                           |                  |                 |                 |
| <55                                    | 2.847 (0.626-12.952)      | 0.176            | 2.927 (0.651-13.172) | 0.162            |
| ≥55                                    |                           |                  |                 |                 |
| Sex                                    |                           |                  |                 |                 |
| Female                                 | 2.279 (0.712-7.292)       | 0.165            | 2.322 (0.724-7.449) | 0.156            |
| Male                                   |                           |                  |                 |                 |
| Adipo-R1 Positive                      | 1.092 (0.376-3.173)       | 0.871            | 1.183 (0.406-3.449) | 0.758            |
| Adipo-R2 Positive                      | 1.911 (0.598-6.108)       | 0.274            | 2.03 (0.635-6.490) | 0.232            |
| Tumor Localisation                     |                           |                  |                 |                 |
| Rectum                                 | 1.158 (0.352-3.817)       | Reference category | 1.227 (0.372-4.050) | 0.737            |
| Sigmoid colon                          | 2.133 (0.248-18.341)      | 0.49             | 2.206 (0.256-18.983) | 0.471            |
| Descending colon                       | 0.424 (0.082-2.194)       | 0.306            | 0.456 (0.088-2.358) | 0.349            |
| Right colon                            |                           |                  |                 |                 |
| Pathological stage (TNM)               |                           |                  |                 |                 |
| Stage 1+ Stage 2                       | 1.158 (0.352-3.817)       | Reference category | 1.227 (0.372-4.050) | 0.737            |
| Stage 3+ Stage 4                       |                           | 0.021            | 10.042 (1.313-76.802) | 0.026            |
| N stage                                |                           |                  |                 |                 |
| N0                                     | 4.623 (1.03-20.68)        | 0.045            | 4.25 (1.952-19.023) | 0.043            |
| N1+N2                                  |                           |                  |                 |                 |
| Metastasis (M) stage                   |                           |                  |                 |                 |
| M0                                     | 12.844 (3.844-42.911)     | Reference category | 8.936 (2.895-27.583) | <0.0001          |
| M1                                     |                           | <0.0001          |                 |                 |
| Duke’s classification                  |                           |                  |                 |                 |
| A+B                                    | 11.004 (1.438-84.2)       | Reference category | 10.042 (1.313-76.802) | 0.026            |
| C+D                                    |                           | 0.021            |                 |                 |
| Differentiation                        |                           |                  |                 |                 |
| Well                                    | 1.138 (0.317-4.093)       | Reference category | 1.075 (1.300-3.856) | 0.912            |
| Moderate+ Poor                         |                           | 0.843            |                 |                 |
| Perineural invasion                    |                           |                  |                 |                 |
| Absent                                 | 2.911 (1.00-8.784)        | 0.05             | 2.711 (1.898-8.184) | 0.045            |
| Present                                |                           |                  |                 |                 |
| Venous invasion                        |                           |                  |                 |                 |
| Absent                                 | 4.029 (1.261-12.87)       | Reference category | 3.576 (1.119-11.430) | 0.032            |
| Present                                |                           | 0.019            |                 |                 |
| Lymphatic invasion                     |                           |                  |                 |                 |
| Absent                                 | 0.689 (0.214-2.224)       | Reference category | 0.668 (1.207-2.148) | 0.498            |
| Present                                |                           | 0.534            |                 |                 |
| Tumor size                             |                           |                  |                 |                 |
| <5 cm                                  | 0.374 (0.104-1.343)       | Reference category | 4.623 (1.03-20.68) | 0.045            |
| ≥5 cm                                  |                           | 0.131            |                 |                 |
| Recurrence                             |                           |                  |                 |                 |
| Absent                                 | 7.437 (2.527-21.885)      | Reference category | 6.257 (2.141-18.281) | 0.001            |
| Present                                |                           | <0.0001          |                 |                 |
| 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...
clinopathological 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 clinico-pathological 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.

Sugiyma et al. investigated the effects of global 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 (Sugiyma 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; Daney 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 is a limitation in the 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.

References

Ayyildiz T, Dolar E, Ugras N, et al (2014). Lack of any prognostic relationship between adiponectin receptor (Adipo R1/R2) expression for early/advanced stage gastric cancer. Asian Pac J Cancer Prev, 15, 4711-16.

Barresi V, Tucciari G, Barresi G (2009a). Adiponectin immunohistochemical expression in colorectal cancer and its correlation with histological grade and tumour microvessel density. Pathology, 41, 533-8.

Barresi V, Grosso M, Giuffre G, Tucciari G, Barresi G (2009b). The expression of adiponectin receptors Adipo R1 and Adipo R2 is associated with an intestinal histotype and longer survival in gastric carcinoma. J Clin Pathol, 62, 705-9.

Brakenhielm E, Veitomäki N, Cao R, et al (2004). Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci USA, 101, 2476-81.

Byeon JS, Jeong JY, Kim MJ, et al (2010). Adiponectin and adiponectin receptor in relation to colorectal cancer progression. Int J Cancer, 127, 2758-67.

Chen MW, Ye S, Zhao LL, et al (2012). Association of plasma total and high-molecular-weight adiponectin with risk of colorectal cancer: an observational study in Chinese male. Med Oncol, 29, 3129-35.

Cnop M, Havel PJ, Utschneider KM, et al (2003). Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia, 46, 459-69.

Colussi D, Brandi G, Bazzoli F, Ricciardiello L (2013). Molecular pathways involved in colorectal cancer: implications for disease behavior and prevention. Int J Mol Sci, 14, 16365-85.

Dal Maso L, Augustin LS, Karalis A, et al (2004). Circulating adiponectin and endometrial cancer risk. J Clin Endocrinol Metab, 89, 1160-3.

Dalamaga M, Diakopoulos KN, Mantzoros CS (2012). The
role of adiponectin in cancer: a review of current evidence. Endocr Rev, 33, 547-94.

Dancey JE (2002). Clinical development of mammalian target of rapamycin inhibitors. Hematol Oncol Clin North Am, 16, 1101-14.

Fukumoto J, Otake T, Tajima O, et al (2008). Adiponectin and colorectal adenomas: Self Defense Forces Health Study. Cancer Sci, 99, 781-6.

Goldfine AB, Kahn CR (2003). Adiponectin: linking the fat cell to insulin sensitivity. Lancet, 362, 1431-2.

Gonullu G, Kahraman H, Bedir A, et al (2010). Association between adiponectin, resistin, insulin resistance, and colorectal tumors. Int J Colorectal Dis, 25, 205-12.

Gulcelik MA, Colakoglu K, Dincer H, et al (2012). Associations between adiponectin and two different cancers: breast and colon. Asian Pac J Cancer Prev, 13, 395-9.

Ho GY, Wang T, Gunter MJ, et al (2012). Adiponokines linking obesity with colorectal cancer risk in postmenopausal women. Cancer Res, 72, 3029-37.

Huang S, Houghton PJ (2003). Targeting mTOR signaling for cancer therapy. Curr Opin Pharmacol, 3, 371-77.

Ishikawa M, Kitayama J, Kazama S, et al (2005). Plasma adiponectin and gastric cancer. Clin Cancer Res, 11, 466-72.

Joshi RK, Lee SA (2014). Obesity related adipokines and colorectal cancer: a review and meta-analysis. Asian Pac J Cancer Prev, 15, 397-405.

Kadowaki T, Yamauchi T, Kubota N, et al (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest, 116, 1784-92.

Kamada Y, Matsumoto H, Tamura S, et al (2007). Hypoadiponectinemia accelerates hepatic tumor formation in nonalcoholic steatohepatitis mouse model. J Hepatol, 47, 556-64.

Kazumi T, Kawayo H, Sakai K, Hirano T, Yoshino G (2002). Adiponectin and colorectal cancer: a review and meta-analysis. Asian Pac J Cancer Prev, 15, 397-405.

Kadotani T, Yamauchi T, Kubota N, et al (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest, 116, 1784-92.

Kumano A, Soderberg S, Kaaks R, Jellum E, Stattin P (2007). Hypoadiponectinemia accelerates hepatic tumor formation in nonalcoholic steatohepatitis mouse model. J Hepatol, 47, 556-64.

Goldfine AB, Kahn CR (2003). Adiponectin: linking the fat cell to insulin sensitivity. Lancet, 362, 1431-2.

Gonullu G, Kahraman H, Bedir A, et al (2010). Association between adiponectin, resistin, insulin resistance, and colorectal tumors. Int J Colorectal Dis, 25, 205-12.

Gulcelik MA, Colakoglu K, Dincer H, et al (2012). Associations between adiponectin and two different cancers: breast and colon. Asian Pac J Cancer Prev, 13, 395-9.

Ho GY, Wang T, Gunter MJ, et al (2012). Adiponokines linking obesity with colorectal cancer risk in postmenopausal women. Cancer Res, 72, 3029-37.

Huang S, Houghton PJ (2003). Targeting mTOR signaling for cancer therapy. Curr Opin Pharmacol, 3, 371-77.

Ishikawa M, Kitayama J, Kazama S, et al (2005). Plasma adiponectin and gastric cancer. Clin Cancer Res, 11, 466-72.

Joshi RK, Lee SA (2014). Obesity related adipokines and colorectal cancer: a review and meta-analysis. Asian Pac J Cancer Prev, 15, 397-405.

Kadowaki T, Yamauchi T, Kubota N, et al (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest, 116, 1784-92.

Kamada Y, Matsumoto H, Tamura S, et al (2007). Hypoadiponectinemia accelerates hepatic tumor formation in nonalcoholic steatohepatitis mouse model. J Hepatol, 47, 556-64.

Kazumi T, Kawayo H, Sakai K, Hirano T, Yoshino G (2002). Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with normal blood pressure. Diabetes Care, 25, 971-6.

Kelesidis I, Kelesidis T, Mantzoros CS (2006). Adiponectin and cancer: a systematic review. Br J Cancer, 94, 1221-5.

Kojima S, Kojima S, Maruyoshi H, et al (2011). Hypercholesterolemia and hypo-adiponectinemia are associated with necrotic core-rich coronary plaque. Int J Cardiol, 147, 371-6.

Kumor A, Daniel P, Pietrzkucz M, Malecka-Panas E (2009). Serum leptin, adiponectin, and resistin concentration in colorectal adenoma and carcinoma (CC) patients. Int J Colorectal Dis, 24, 275-81.

Lukanova A, Soderberg S, Kaaks R, Jellum E, Stattin P (2006). Serum adiponectin is not associated with risk of CRC. Cancer Epidemiol Biomarkers Prev, 15, 401-2.

Mantzoros C, Petridou E, Dasypritis N, et al (2004). Adiponectin and breast cancer risk. J Clin Endocrinol Metab, 89, 1102-7.

Matsuzawa Y, Shimomura I, Kihara S, et al (2003). Importance of adipocytokines in obesity-related diseases. Horm Res, 3, 56-9.

Michalaks K, Williams CJ, Mitsiades N, et al (2007). Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: a case control study. Cancer Epidemiol Biomarkers Prev, 16, 308-13.

Moore LL, Bradlee ML, Singer MR, et al (2004). BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes Relat Metab Disord, 28, 559-67.

Murphy TK, Calle EE, Rodriguez C, et al (2000). Body mass index and colon cancer mortality in a large prospective study. Am J Epidemiol, 152, 847-54.

Oldham S, Hafen E (2003). Insulin/IGF-1 and target of rapamycin signaling: a TOR de force in growth control. Trends Cell Biol, 13, 79-85.

Otake S, Takeda H, Suzuki Y, et al (2005). Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clin Cancer Res, 11, 3642-6.

Ouchi N, Kihara S, Arita Y, et al (1999). Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation, 100, 2473-6.

Ouchi N, Kihara S, Arita Y, et al (2001). Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation, 103, 1057-63.

Philp AJ, Campbell IG, Leet C, et al (2001). The phosphatidylinositol 3'-kinase p85alpha gene is an oncogene in human ovarian and colon tumors. Cancer Res, 61, 7426-29.

Rodrigues VS, Milanski M, Fagundes JJ, et al (2012). Serum levels and mesenteric fat tissue expression of adiponectin and leptin in patients with Crohn’s disease. Clin Exp Immunol, 170, 558-64.

Saxena A, Baliga MS, Ponomene V, et al (2013). Mucus and adiponectin deficiency: role in chronic inflammation-induced colon cancer. Int J Colorectal Dis, 28, 1267-79.

Siegel R, Desantis C, Virgo K, et al (2012). Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin, 62, 220-41.

Vogt PK (2001). PI 3-kinase, mTOR, protein synthesis and cancer. Trends Mol Med, 7, 482-4.

Wei EK, Giovannucci E, Fuchs CS, Willet WC, Mantzoros CS (2005). Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. J Natl Cancer Inst, 97, 1688-94.

Williams CJ, Mitsiades N, Sozopoulos E, et al (2008). Adiponectin receptor expression is elevated in colorectal carcinomas but not in gastrointestinal stromal tumors. Endocr Relat Cancer, 15, 289-99.

Wolpin BM, Mayer RJ (2008). Systemic treatment of colorectal cancer. Gastroenterol, 134, 1296-10.

Yamauchi T, Kamon J, Ito Y, et al (2003). Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature, 423, 762-9.

Yang WS, Lee WJ, Funahashi T, et al (2002). Plasma adiponectin levels in overweight and obese Asians. Obes Res, 10, 1104-10.

Yoneda K, Tomimoto A, Endo H, et al (2008). Expression of adiponectin receptors, Adipo-R1 and Adipo-R2, in normal colon epithelium and colon cancer tissue. Oncol Rep, 20, 479-83.