



Leptin and peroxisome proliferator-activated receptor γ expression in colorectal adenoma

Hyung Hun Kim, You Sun Kim, Yun Kyung Kang, Jeong Seop Moon

Hyung Hun Kim, You Sun Kim, Jeong Seop Moon, Department of Internal Medicine, Seoul Paik Hospital, Inje University College of Medicine, Seoul 100-032, South Korea
Yun Kyung Kang, Department of Pathology, Seoul Paik Hospital, Inje University College of Medicine, Seoul 100-032, South Korea

Hyung Hun Kim, Department of Internal Medicine, Kosin University College of Medicine, Busan 602-702, South Korea

Author contributions: Kim HH performed data analysis and wrote this paper; Kim YS guided the conception and design of this paper and revising it critically for important intellectual content; Kang YK was responsible for leptin and PPARG immunohistochemical staining and performed the interpretation of data; Moon JS supported the acquisition of data.

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Correspondence to: You Sun Kim, MD, Department of Internal Medicine, Seoul Paik Hospital, Inje University College of Medicine, 85 2-Ga, Jeo-Dong, Jung-Gu, Seoul 100-032, South Korea. yousunk69@korea.com

Telephone: +82-2-22700012 Fax: +82-2-22794021

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expression was more frequently observed in intermediate/high grade dysplasia than in low grade dysplasia ($P = 0.030$). However, PPARG expression was not correlated with BMI and grade of dysplasia.

CONCLUSION: BMI has influenced on the leptin expression of colorectal adenoma. The exact mechanism underlies the strong correlation between leptin and PPARG expression needs further study.

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Key words: Leptin; Peroxisome proliferator-activated receptor γ ; Obesity; Body mass index; Colorectal adenoma

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Abstract

AIM: To investigate the expressions of leptin and peroxisome proliferator-activated receptor γ (PPARG) in relation to body mass index (BMI).

METHODS: We evaluated leptin and PPARG expression in 30 adenomas over 1 cm in size by immunohistochemical staining. In addition, clinicopathologic features including BMI were assessed.

RESULTS: PPARG and leptin expression showed a strong positive correlation ($P = 0.035$). The average BMI of the leptin-positive group was higher than that of the leptin-negative group ($25.4 \pm 3.4 \text{ kg/m}^2$ vs $22.6 \pm 2.4 \text{ kg/m}^2$, $P = 0.018$), and leptin expression was significantly correlated with high BMI ($P = 0.024$). Leptin

INTRODUCTION

Colorectal cancer is a major cause of cancer-related mortality and morbidity^[1]. Many Asian countries, including South Korea, China, Japan, and Singapore, have experienced an increase of 2 to 4 times in the incidence of colorectal cancer during the past few decades^[2]. Obesity is a risk factor of colorectal cancer and colorectal adenoma, and is an independent poor prognostic variable in colorectal cancer survivors^[3-5]. Although mechanism by which obesity increases the risk of colorectal cancer is not clearly understood, obesity-induced changes in hormonal metabolism are known to distort the normal balance between cell proliferation, differentiation, and apoptosis.

tosis^[3]. Circulating levels of insulin, insulin-like growth factor, and leptin are increased in obesity and may mediate the increased risk of colorectal cancer^[6,7]. Leptin plays a central role in mammalian feeding behavior and energy expenditure^[8]. In addition to its neurohormonal action in the brain, several *in vitro* studies have shown that leptin can act as a mitogenic, antiapoptotic, and tumorigenic factor for different cancer cell lines^[9,10]. Moreover, leptin is overexpressed in human colorectal cancer^[11], and its expression gradually increases during the transition from normal adenoma to adenocarcinoma, suggesting that it is associated with colorectal carcinogenesis^[12]. Interestingly, however, high leptin expression in colorectal cancer is an indicator of favorable tumor features and better survival in colorectal cancer patients^[12]. One interesting fact revealed in our previous study was that there was a linear trend between leptin expression of colorectal adenomas and patients' body mass index (BMI)^[13]. This suggests that obesity postulated from high BMI can affect tumorigenesis through local leptin activity.

Peroxisome proliferator-activated receptor γ (PPARG) is a member of the nuclear hormone receptor PPAR superfamily^[14]. PPARG plays an important role in adipose cell differentiation, modulation of metabolism, modulation of the inflammatory response, and cellular apoptosis^[15,16]. Unlike leptin, PPARG is involved in cell cycle regulation and cellular differentiation in colonic epithelium, supporting its antineoplastic effect^[15,17,18]. Therefore, some researchers have tried to use PPARG agonists as chemotherapeutic agents for malignancy^[19]. Moreover, the overexpression of PPARG in colorectal cancer is independently correlated with longer survival of patients, so PPARG expression appears to mark an indolent subset of colorectal cancers as does leptin expression^[20].

Despite the antagonistic effects on the development of neoplasm, the expressions of PPARG and leptin are related with favorable prognosis respectively^[12,20]. This phenomenon led us consider the possible interaction of PPARG and leptin in the development of colon cancer and adenoma. Colorectal adenoma is the well known premalignant lesion of colorectal cancer, and remove of it is accepted as a most effective prevention of colorectal cancer. However, there are only few studies regarding leptin and PPARG expression in colorectal adenoma^[12]. Moreover, there has been no report about the correlation between leptin expression and PPARG expression. Therefore, we aimed to investigate leptin and PPARG expression in colorectal adenomas in relation to BMI. We also investigated whether the detailed characteristics of adenomas such as dysplasia grade, number, and location, are correlated with leptin or PPARG expression. Finally, we aimed to establish whether the expression of leptin is correlated with that of PPARG in colorectal adenomas.

MATERIALS AND METHODS

Patients and specimens

Thirty patients with colorectal adenomas of over 1 cm

in size were enrolled in this study. All patients, less than 55 years old, were diagnosed and treated by polypectomy or endoscopic mucosal resection at the Seoul Paik Hospital (Seoul, South Korea) between August 2007 and August 2008. We excluded adenomas, which had carcinomatous components. All tissue samples were formalin fixed and paraffin embedded. Hematoxylin and eosin (HE) slides, pathologic reports, and medical records were retrospectively reviewed to confirm the diagnosis and clinicopathologic parameters including age, gender, BMI, adenoma location, adenoma size, pathologic type, and dysplasia grade. We followed the guidelines for human studies and animal welfare regulations. Subjects had given their informed consent, and the study protocol had been approved by the institutional review board on human research.

Tissue microarray construction

The most representative area of each adenoma was carefully selected and marked on a HE stained slide. Core tissue biopsies (2 mm in diameter) were taken from the corresponding donor blocks and arranged in a new recipient paraffin block (tissue array block) using a trephine apparatus (SuperBioChips Laboratories, Seoul, South Korea). Duplicate tissue cores were taken from each donor block to minimize the limitations of identifying a representative area of the tumor.

Immunohistochemical staining

Serial 4- μ m thick sections of tissue array blocks were examined immunohistochemically. Sections were deparaffinized, and antigen retrieval was performed in 10 mmol/L sodium citrate buffer (pH 6.0) for 15 min at 95 °C using a microwave oven. Endogenous peroxidase was blocked for 10 min with 30 mL/L H₂O₂ and slides were labeled with a mouse monoclonal antibody to PPARG (E-8, 1/50 dilutions; Santa Cruz Biotechnology, Santa Cruz, CA, United States) or a rabbit polyclonal antibody to leptin (A-20, 1/100 dilution; Santa Cruz Biotechnology) for 1 h. After washing with phosphate-buffered saline, a chromogen reaction was carried out using an Ultravision LP kit (Labvision, Fremont, CA, United States). Briefly, sections were incubated with primary antibody enhancer for 20 min and horseradish peroxidase for 30 min. 3, 3'-diaminobenzidine tetrahydrochloride was used as a chromogen and Mayer's hematoxylin counterstain was applied. Negative controls without primary antibody were run simultaneously. The expressions of both proteins were evaluated based on the intensity and extent of the staining. Staining intensity was scored as 0 (negative), 1 (weak), or 2 (strong). Extent of staining was scored as 0 (0%), 1 (1%-20%), 2 (20%-50%), or 3 (50%-100%). PPARG positivity was defined as the presence of weak nuclear staining in at least 20% of adenoma cells, or the presence of strong nuclear staining (Figure 1A and B). Leptin positivity was defined as the presence of weak cytoplasmic staining in at least 20% of adenoma cells, or the presence of strong cytoplasmic staining (Figure 1C and D).

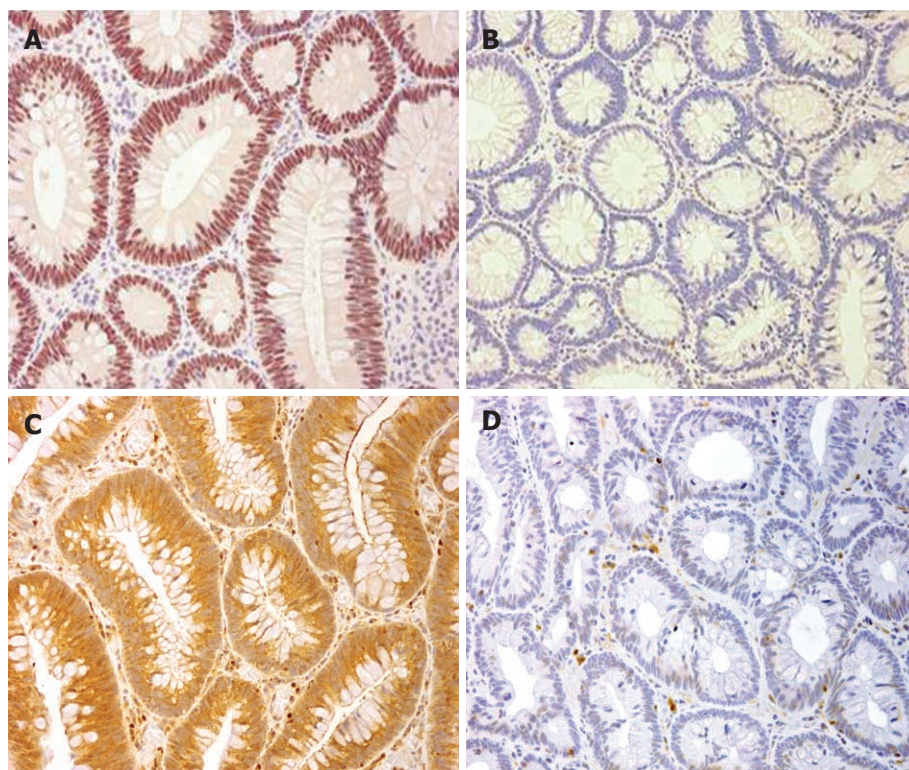


Figure 1 Immunohistochemical detection of peroxisome-proliferator-activated receptor γ and leptin expression in colorectal adenomas. A and B: Strong nuclear expression of peroxisome-proliferator-activated receptor γ (PPARG) (A) and negative expression (B) in representative colorectal adenomas; C and D: Strong cytoplasmic expression of leptin (C) and negative expression (D) in representative colorectal adenomas. Original magnification: $\times 200$ (A-D).

Table 1 Baseline characteristics of subjects

Baseline characteristics	Value
Total patients	30
Sex (male) <i>n</i> (%)	23 (77)
Age, year	44.6 ± 6.5
BMI (kg/m^2)	24.2 ± 3.83
Polyp size (cm)	1.2 ± 0.3
Polyp number	2.2 ± 1.4
Location ¹ <i>n</i> (%)	
Left colon	17 (56.7)
Right colon	13 (43.3)
Dysplasia grade <i>n</i> (%)	
Low	13 (43.3)
Intermediate/high	17 (56.7)
Pathology <i>n</i> (%)	
Tubular	25 (83.0)
Villotubular	5 (17.0)

¹Left colon consists of transverse, descending and sigmoid colon and rectum, and right colon is composed of cecum and ascending colon. BMI: Body mass index.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 12.0, SPSS, Chicago, IL, United States). The relationship between PPARG and leptin was evaluated using the Fisher's exact test. The relationships of PPARG or leptin with clinicopathologic features were investigated by the Fisher's exact test and *t* test. Two tailed *P* values less than 0.05 were regarded as statistically significant.

RESULTS

The study sample included 23 male and 7 female patients. Patient age ranged from 29 to 53 years (44.6 ± 6.5 years). Tumors consisted of 25 tubular adenomas and 5 villotubular adenomas. Seventeen adenomas located in the left colon: transverse, descending and sigmoid colon and rectum, and 13 adenomas located in the right colon: cecum and ascending colon. The sizes of adenomas ranged from 1 to 2.5 cm (1.2 ± 0.3 cm). The number of polyps ranged from 1 to 5 (2.2 ± 1.4). Thirteen adenomas showed low grade dysplasia. Seventeen adenomas had intermediate grade dysplasia or high grade dysplasia. There were no polyps containing carcinoma-*in-situ*. These results were described in Table 1.

In colorectal adenomas, 22 of 30 cases (73.3%) showed PPARG expression, and 17 cases (56.7%) showed leptin expression (Table 2; representative photomicrographs in Figure 1). PPARG and leptin expression showed significant correlation each other ($P = 0.035$).

The BMI of the leptin positive group ($25.4 \pm 3.4 \text{ kg}/\text{m}^2$) was significantly higher than that of the leptin negative group ($22.6 \pm 2.4 \text{ kg}/\text{m}^2$, $P = 0.018$, Figure 2A), and leptin expression was significantly correlated with high BMI ($\geq 25 \text{ kg}/\text{m}^2$, $P = 0.024$, Table 2). In contrast, PPARG expression was not correlated with BMI ($P = 0.162$, Figure 2B).

Leptin expression was observed more frequently in the intermediate/high grade dysplasia group than in the low ($P = 0.030$, Table 2). However, PPARG expression was not

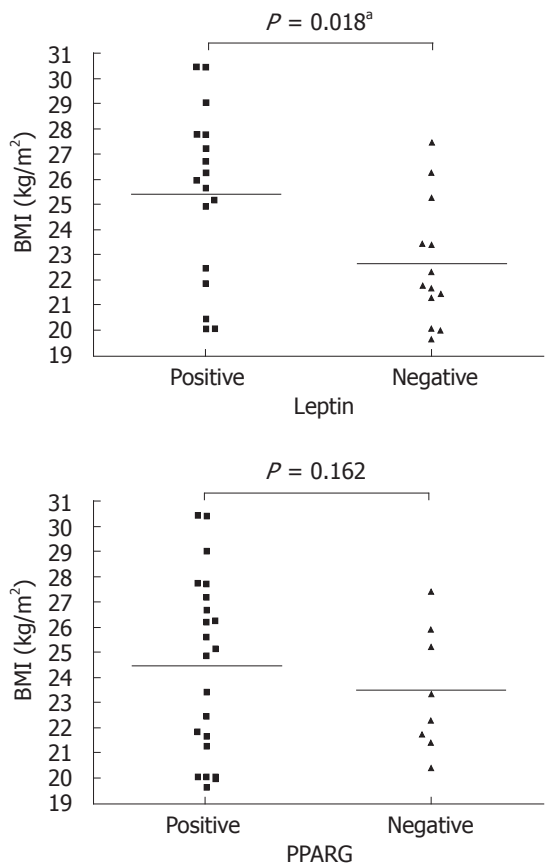


Figure 2 Leptin and peroxisome-proliferator-activated receptor γ expression in colorectal adenomas and body mass index. A: The body mass index (BMI) of leptin positive group (25.4 ± 3.4 kg/m²) was significantly higher than the BMI of leptin negative group (22.6 ± 2.4 kg/m², $P = 0.018$); B: There is no significant difference between the BMI of peroxisome-proliferator-activated receptor γ (PPARG) positive group (24.47 ± 0.75 kg/m²) and PPARG negative group (23.52 ± 0.87 kg/m², $P = 0.162$).

correlated with dysplasia grade ($P = 0.295$, Table 2). Neither leptin nor PPARG expression were correlated with the location or pathologic types of adenomas (Table 2).

DISCUSSION

Our study revealed a strong correlation between leptin expression in colorectal adenomas and high BMI. Although BMI is just one measure of obesity, the strong correlation between high BMI and leptin expression nonetheless suggests that obesity may influence leptin expression in adenomas. In our previous study, we found a trend between leptin expression and BMI^[13]. However, when we enrolled colorectal adenoma larger than 1 cm size in this study, we could observe the strong correlation between high BMI and leptin expression in colorectal adenomas.

Several studies of leptin expression in cancers have suggested that local rather than endocrine leptin might play a significant role in breast tumorigenesis^[21]. More specifically, both leptin and leptin receptor were found in breast tumors, indicating that leptin could influence cancer cells through autocrine or paracrine mechanisms^[21-23].

Table 2 Leptin expression in colorectal adenomas and clinicopathologic characteristics of patients <i>n</i> (%)						
Clinicopathologic features	Leptin expression			PPARG expression		
	Positive	Negative	<i>P</i> value	Positive	Negative	<i>P</i> value
BMI	17 (56.7)	13 (43.3)		22 (73.3)	8 (26.7)	
≥ 25 kg/m ²	11 (36.7)	3 (5.0)	0.024	11 (36.7)	3 (9.9)	0.689
< 25 kg/m ²	6 (20.0)	10 (33.3)		11 (36.7)	5 (16.7)	
Dysplasia grade						
Low	5 (16.7)	9 (30.0)	0.03	9 (29.7)	5 (16.7)	0.295
Intermediate/high	12 (40.0)	4 (13.3)		13 (43.7)	3 (9.9)	
Location ¹						
Left colon	11 (36.7)	6 (20.0)	0.794	8 (26.7)	3 (9.9)	0.954
Right colon	6 (20.0)	4 (13.3)		14 (46.7)	5 (16.7)	
Histological type						
Tubular	14 (46.7)	11 (36.7)	0.869	12 (40.0)	13 (43.4)	0.743
Villotubular	3 (10.0)	2 (6.6)		2 (6.7)	3 (9.9)	

¹Left colon consists of transverse, descending and sigmoid colon and rectum, and right colon is composed of cecum and ascending colon. BMI: Body mass index; PPARG: Peroxisome proliferator-activated receptor γ .

However, given the induction of leptin overexpression by obesity-related stimuli, it is reasonable to also consider systemic effects on leptin expression^[23].

Several studies have suggested that leptin expression is related to local hypoxia. Indeed, in several cellular systems, including breast cancer cells, leptin mRNA expression is induced by hypoxia, and the leptin gene promoter is regulated by hypoxia-inducible factor-1 α ^[23-25]. However, we would argue that high BMI is a more likely potential marker for leptin expression than hypoxia in colorectal adenomas, for the following 2 reasons. First, previous studies regarding leptin expression and hypoxia dealt with cancers rather than adenomas. It is reasonable to accept that leptin is induced under the effect of hypoxia in cancers due to their large mass, but colorectal adenomas are much smaller than typical cancers. Furthermore, PPARG expression was strongly correlated with leptin expression in our study. PPARG levels are known to be reduced by hypoxia^[26], so the strong correlation between leptin and PPARG further suggests that leptin expression is probably not caused by hypoxia in colorectal adenomas.

When we divided adenomas into low and intermediate/high dysplasia grade groups, leptin was expressed more frequently in the intermediate/high grade dysplasia group. Interestingly, the ratio of overexpressed leptin was gradually increased from normal mucosa, to adenoma, to carcinoma^[11,12]. Therefore, increased leptin expression ratio from low grade to intermediate/high grade dysplasia appears to follow the pattern of increased leptin expression from normal mucosa to adenoma, to carcinoma by stages. Moreover, this may connote that as dysplasia progresses, autocrine or paracrine mechanisms of leptin may thus be progressively enhanced in colorectal adenomas.

In our study, PPARG expression was positively correlated with leptin expression in colorectal adenomas, but was not correlated with high BMI or adenoma dysplasia grade. PPARG and leptin functionally intersect *via* the Ja-

nus-activated kinase/signal transducers and activators of transcription (JAK/STAT) pathway. Leptin signaling is transmitted mainly by the JAK/STAT pathway^[27] and terminated by the induction of suppressor of cytokine signaling-3^[28]. In contrast to leptin, PPARG agonists inhibit cytokine-induced activation of the JAK-STAT pathway^[29] and STAT-3^[30]. These findings show that leptin and PPARG clearly affect the JAK/STAT pathway in different ways and possibly interact each other by unrevealed feedback mechanisms^[31]. Regarding 2 molecules, several recent studies revealed that leptin might exert an inhibitory effect on PPARG protein expression. Zhou *et al.*^[32] suggested leptin induced extracellular signal-regulated kinases (ERK) 1/2 activation, which cause the subsequent decline in PPARG expression in hepatic stellate cells. In addition, leptin could inhibit the PPARG expression in TallyHo/Jng mouse^[33]. On the other hands, PPARG ligands has the inhibitory effect on leptin induced hepatic stellate cells proliferation through the reversion of ERK 1/2 activation^[33,34]. However, molecules may interact *via* different mechanism or interact with each other differently depend on cells or organs. Therefore, to clarify the exact mechanism between leptin and PPARG in colorectal adenomas, we think that additional in vitro studies are needed.

There were several limitations in our study. First of all, enrolled numbers in this study was relatively small. We wanted exclude the age factor which strongly influence on development of colorectal adenoma and carcinoma. Indeed, the prevalence of colorectal adenoma in Korea revealed that most colorectal adenomas were detected in aged group^[35]. To determine the pure effect of obesity on leptin and PPARG expression in colorectal adenomas, we enrolled the patients who were under age of 55. However, information from 30 cases was enough to generate appropriate statistical values. Second, limitation was that we were able to investigate the only one indicator of obesity, BMI. Other variables accessing obesity such as waist circumference and waist-hip ratio were not investigated due to lack of information. Third, we did not investigate a control group. If we had evaluated leptin and PPARG expression in hyperplastic polyps or normal mucosa, we would establish specific criteria for the overexpression of 2 molecules in the present study. Fourth, there was no in vitro study about the interaction of PPARG and leptin. These two molecules may affect the JAK/STAT or ERK 1/2 pathways in different ways and possibly interact each other by unrevealed mechanisms. In this study, however, we did not evaluate the mechanism regarding the relationship of leptin and PPARG expression in the development of colorectal adenoma. Our study suggested the correlation between PPARG and leptin expression but could not explain the causal relationship. For understanding the causal relationship, in vitro study should be performed in the near future.

In summary, our study is the first to evaluate simultaneous leptin and PPARG expression in colorectal adenomas in relation to BMI and characteristics of adenomas.

Based on the strong correlation between leptin expression and high BMI, we postulated that energy accumulation might induce overproduction of leptin in colorectal adenomas. The known positive correlation between leptin expression and dysplasia grade further strengthens the possibility that leptin might contribute to the sequential progression of carcinogenesis from low grade dysplasia to colorectal carcinoma and through high grade dysplasia^[11,12]. In contrast, PPARG expression showed no correlation with high BMI or dysplasia grade in colorectal adenomas. The correlation between leptin and PPARG expression suggests that a possible interaction between these 2 molecules during the development of adenomas, likely mediated by the JAK/STAT or ERK 1/2 pathway.

COMMENTS

Background

Colorectal cancer is a major cause of cancer-related mortality and morbidity. Leptin regarded to be associated with colorectal carcinogenesis. Unlike leptin, peroxisome-proliferator-activated receptor γ (PPARG) is involved in antineoplastic effect. Despite the antagonistic effects on the development of neoplasm, the expressions of PPARG and leptin are related with favorable prognosis respectively. This phenomenon suggests that the possible interaction of PPARG and leptin in the development of colon cancer and adenoma.

Research frontiers

Mechanism of leptin expression was one imperative issue in the research field related to the article. Obesity, expressed as body mass index (BMI), can be related with leptin expression in colorectal adenomas. Second issue was the relationship between PPARG expression and leptin expression in colorectal adenomas because these two molecules behave antagonistically.

Innovations and breakthroughs

The study is the first to evaluate simultaneous leptin and PPARG expression in colorectal adenomas in relation to BMI and characteristics of adenomas. Based on the strong correlation between leptin expression and high BMI, we postulated that energy accumulation might induce overproduction of leptin in colorectal adenomas. The correlation between leptin and PPARG expression suggests a possible interaction between these 2 molecules during the development of adenomas, likely mediated by the janus-activated kinase / signal transducers and activators of transcription or extracellular signal-regulated kinase 1/2 pathway.

Applications

Present study showed the first step to widen our understating about the interaction of PPARG and leptin in the development of colorectal adenomas. New findings about this molecular interaction can be applicable in the prevention of colorectal adenomas, premalignant lesion of colorectal cancer, and can provide pivotal hint for chemotherapy for colorectal cancer.

Peer review

The paper demonstrated interesting findings. Strong correlation between leptin and PPARG expression in colorectal adenomas, correlation between leptin expression and high BMI, and Leptin expression was more frequently observed in intermediate/high grade dysplasia than in low grade dysplasia, while PPARG expression was not correlated with BMI or grade of dysplasia.

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