Int J Clin Exp Pathol 2016;9(11):11774-11780
www.ijcep.com /ISSN:1936-2625/IJCEP0040048

Original Article

Leptin expression in stromal cells of endometrial carcinomas is associated with advanced stage and disease recurrence

Mohamad Nidal Khabaz[1], Nadeem Shafique Butt[2], Basim Al-Maghrabi[3], Nisrin Anfinan[4], Khalid Sait[4], Jaudah Al-Maghrabi[5]

[1]Department of Pathology, [2]Department of Family and Community Medicine, Rabigh Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [3]Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [4]Department of Obstetrics and Gynecology, Gynecology Oncology Unit, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [5]Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Received September 14, 2016; Accepted September 27, 2016; Epub November 1, 2016; Published November 15, 2016

Abstract: This study investigates the relation between leptin expression and the clinicopathological parameters in endometrial carcinomas. Seventy-one cases of previously diagnosed endometrial carcinoma (including 59 endometrioid adenocarcinomas, 9 serous carcinomas, 1 clear cell adenocarcinoma, and 2 malignant mixed Mullerian tumors) and 30 tissue samples of non-cancerous endometrium (including 16 proliferative endometrium, 10 secretory endometrium and 4 endometrial polyps) were employed for leptin detection using tissue microarrays and immunostaining. A total number of 48 (67.6%) cases were positive for leptin immunostaining. Brown granular cytoplasmic expression of leptin was detected in almost 68% of endometrioid adenocarcinomas, 66.7% serous carcinomas. Twenty-one (70%) control cases showed granular cytoplasmic expression. Positive leptin immunostaining was found more frequent in transformed epithelial cells and stromal cells of endometrioid adenocarcinomas and serous carcinomas respectively, showing significant statistical association (*P*-value = 0.005). Tumor stage is also significantly associated with cell type leptin immunoreactivity (*P*-value = 0.007), a considerable fraction of stage II is associated with leptin immunostaining of transformed epithelium whereas leptin immunoreactivity in endometrial stromal cells is more frequent in stage III. Disease recurrence rate is significantly higher in patients whom endometrial stromal cells are positive for leptin immunostaining (*P*-value = 0.000). Poor survival status (death) is also significantly associated with a group of patients whom endometrial stromal cells showed positive leptin immunoreactivity (*P*-value = 0.000). Our results confirm the diagnostic and prognostic values of leptin in supporting the diagnosis and prognosis of endometrial carcinomas. These preliminary findings recommend that leptin may be a valuable marker for predicting histotype, stage, recurrence and poor prognosis in endometrial carcinoma.

Keywords: Leptin, endometrial carcinoma, immunohistochemistry

Introduction

Endometrial carcinomas are common aggressive malignant neoplasms of the female reproductive organs [1]. There are considerable differences between the main histological types of endometrial carcinomas regarding a group of factors that may influence patient treatment such as prognosis, pattern of recurrence, and chemotherapeutic response [2-4]. Therefore, distinction between endometrial carcinoma histotypes is necessary. Thus, an immunohistochemical marker for differentiating histotypes of endometrial carcinomas and its prognosis is certain to be valuable.

Leptin is a 167 amino acids protein that is encoded by the Obese (Ob) gene. Although it has been produced originally in white adipose tissue, other tissues have appeared to express leptin such as the placenta, ovaries, liver, stomach, skeletal muscles and pituitary gland [5-7]. It is now believed to have multiple functions and considered a member of adipokines, which play a significant role in lipogenesis, metabolism, inflammatory process, glucose homeosta-

Table 1. Clinicopathological characteristics of endometrial carcinoma patients

Clinicopathological parameters		Leptin immunostaining						*P*-Value
		Negative stain		Cases with positive stain in epithelial cells only		Cases with positive stain in stromal and epithelial cells		
		Count	%	Count	%	Count	%	
Age in Years	< 40	1	20.0%	3	60.0%	1	20.0%	0.487
	40-49	5	25.0%	8	40.0%	7	35.0%	
	50-59	10	41.7%	8	33.3%	6	25.0%	
	60-69	4	26.7%	6	40.0%	5	33.3%	
	≥ 70	3	42.9%	3	42.9%	1	14.3%	
Histotype	Endometrioid adenocarcinoma	19	32.2%	27	45.8%	13	22.0%	0.005
	Serous carcinoma	3	33.3%	0	0.0%	6	66.7%	
	Clear cell carcinoma	0	0.0%	1	100.0%	0	0.0%	
	MMMT	1	50.0%	0	0.0%	1	50.0%	
Grade	I	13	32.5%	19	47.5%	8	20.0%	0.259
	II	8	34.8%	8	34.8%	7	30.4%	
	III	1	16.7%	1	16.7%	4	66.7%	
	Ungraded	1	50.0%	0	0.0%	1	50.0%	
Stage	I	12	30.8%	20	51.3%	7	17.9%	0.007
	II	2	40.0%	3	60.0%	0	0.0%	
	III	2	22.2%	0	0.0%	7	77.8%	
	IV	2	66.7%	0	0.0%	1	33.3%	
	Unstaged	5	33.3%	5	33.3%	5	33.3%	
Differentiation	W	13	31.7%	20	48.8%	8	19.5%	0.155
	M	8	40.0%	6	30.0%	6	30.0%	
	P	1	12.5%	2	25.0%	5	62.5%	
	NA	1	50.0%	0	0.0%	1	50.0%	
Recurrence	No	19	33.9%	28	50.0%	9	16.1%	0.000
	Yes	4	26.7%	0	0.0%	11	73.3%	
Alive	No	7	41.2%	0	0.0%	10	58.8%	0.000
	Yes	16	29.6%	28	51.9%	10	18.5%	

sis, reproduction, tissue remodeling, bone formation, immune response, and neoangiogenesis [8-12]. Many studies have reported that leptin promotes tumor cells proliferation, invasion, migration, and inhibit apoptosis via several routes [11, 13-18]. Other studies have investigated leptin role in several tumors development risk including endometrial cancer, but the findings are controversial [19-22]. Certainly undoubted evidence is desirable to clarify leptin's precise role in the development and progression of endometrial carcinomas because recognition of the association between leptin and endometrial tumors can enhance our perception of endometrial carcinogenesis and help developing treatment and preventive plans. Therefore, the current study describes the immunohistochemical phenotype of leptin in endometrial tumors, examines the relation between the expression pattern of leptin and the clinicopathological parameters and follow-up data of these tumors.

Material and methods

Seventy-one paraffin blocks of previously diagnosed endometrial carcinoma were retrieved from the archives of Pathology Department at King Abdulaziz University, Jeddah, Saudi Arabia. Thirty samples of endometrial tissue from benign conditions were also recruited as a control group. These cases covered the period from January 2001 to December 2012. Four micron thickness sections were sliced from paraffin blocks, then stained with hematoxylin and eosin for tumors histopathological characteris-

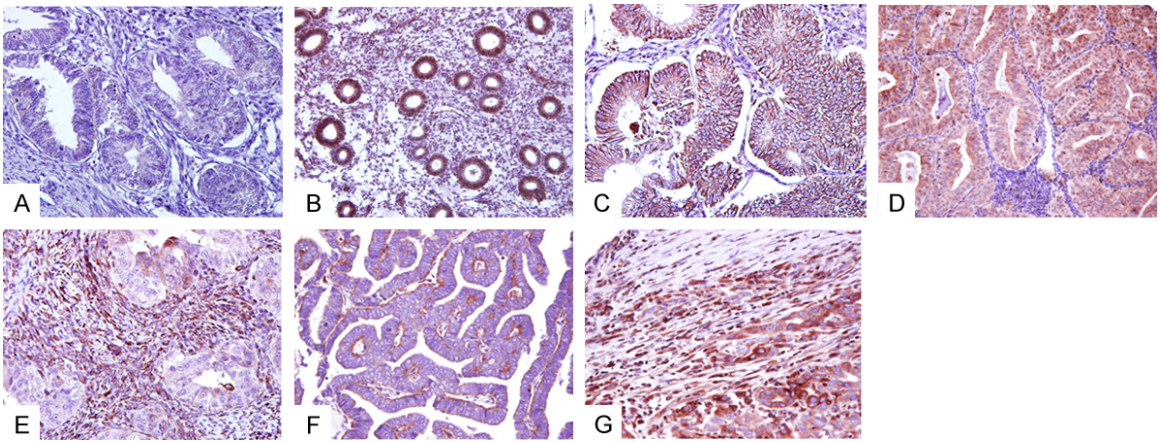

Figure 1. Granular cytoplasmic leptin expression pattern in endometrial tumors. A. Negative stained endometrial adenocarcinoma (40 ×); B. Strong positive stained normal endometrial tissue (20 ×); C. Strong positive staining in epithelial cells of endometrioid adenocarcinoma (40 ×); D. Moderate positive staining in epithelial cells of endometrioid adenocarcinoma (40 ×). E. Strong positive staining in stromal cells and weak/absence in epithelial cells of endometrioid adenocarcinoma; F. Strong positive staining in the apex of epithelial cells of endometrioid adenocarcinoma; G. Strong positive staining in stromal and epithelial cells of serous carcinoma.

tics evaluations, grading, and staging. Patient's clinical data (age, type of carcinoma, size, grade and stage of carcinoma) were extracted from the patient's medical records and listed in **Table 1**. Control cases were chosen from individuals who were curetted for non-cancerous conditions comprising 16 proliferative endometrium, 10 secretory endometrium and 4 endometrial polyps. The mean age of control group was 35.6 years, ranging from 22 to 50 years. All recruited tissue blocks of both benign and malignant conditions were used for tissue microarray construction in the present study. Biomedical Ethical Committee at King Abdulaziz University has approved the present study.

Tissue microarray construction

Seventy-one primary endometrial carcinomas and 30 non-cancerous endometrial tissue samples were used for tissue microarray construction (TMA) as described by Al-Maghrabi and coworkers [23]. Blocks of TMA were cut into 4-micron thickness sections and placed on aminosilane coated slides to be used later in immunohistochemistry.

Immunohistochemistry staining protocol

Immunohistochemical staining of endometrial carcinoma samples, using Ob (A-20) rabbit polyclonal antibody (1:100 dilution; product code: sc-842, Santa Cruz Biotechnology, INC, Dallas, USA), was performed by Multimer technology: ultraViewTM DAB procedure following manufacturer's kit instructions (catalog number: 760-500; Ventana Medical Systems Inc., Arizona, USA). Immunohistochemistry procedure was conducted using Ventana BenchMark ULTRA automatic immunostainer (Ventana Medical Systems Inc., Arizona, USA). Tris-buffered saline replaced the primary antibody in a negative control slide. Placenta tissue section was incorporated as positive internal control. Slides were considered positive when granular brown staining was revealed in the cytoplasm of tumor cells. Leptin immunostaining was scored for intensity of stain by two pathologists using the scoring system of Al-Maghrabi et al., i.e. weak staining +1, moderate +2, and strong +3 [23].

Statistical analysis

Data was statistically analysed using IBM-SPSS version 21. Fisher's exact test is applied to explore the association of leptin immunostaining with various clinicopathological variables. Kaplan-Meier survival curves were used to plot the survival distribution and Log Rank (Mantel-Cox) test is applied to test for equality of survival distributions for the different categories of immunostaining. *P*-value < 0.05 is the statistical significance level.

Results

Seventy-one endometrial neoplastic cases were revised. Clinicopathological parameters

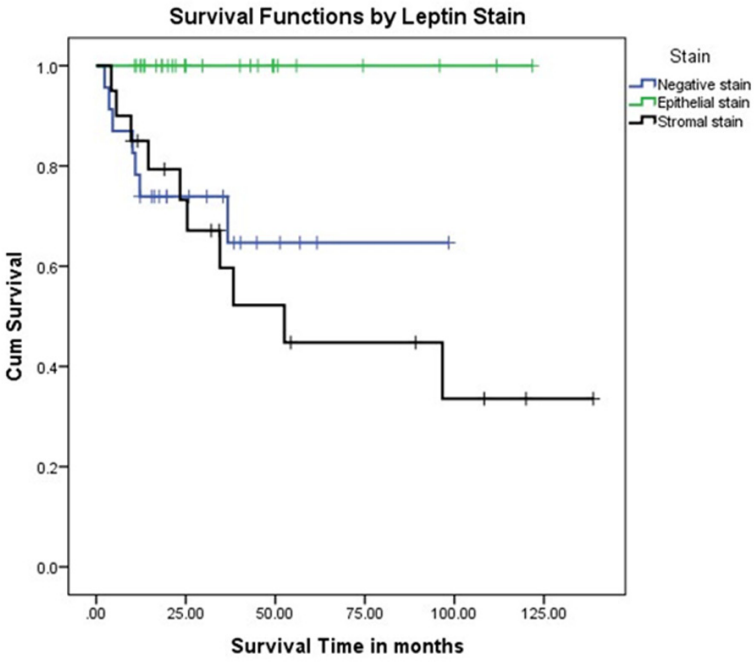

Figure 2. Kaplan Meier survival curves by pattern of leptin immunostaining shows significantly poor survival behavior associated with stromal immunostaining in endometrial carcinoma.

of these tumors have been presented in **Table 1**. The most common type was endometrioid adenocarcinoma and less frequently, papillary serous adenocarcinoma, malignant mixed Mullerian tumors (MMMT) and clear cell carcinoma (**Table 1**). The median age of these cases was 55 years (ranging 26-86 yrs). FIGO histological classification was used for grading endometrial tumors, taking into consideration that the presence of notable nuclear atypia increases the glandular grade by one. Only 50 endometrial tumors have been found to be staged using FIGO staging system. The whole number of mortalities in the full panel of cases was 17 (23.9%). Tumor recurrences were seen in 15 (21.1%) cases (**Table 1**), 10 of these patients are deceased because of their tumor, and the remaining 5 patients were still alive at the latest follow-up.

Positive granular cytoplasmic expression of leptin was detected in 48 (67.6%) cases of endometrial tumors which include 40 endometrioid adenocarcinomas (**Figure 1**) of which 27 (45.8%) cases showed moderate to strong positive immunostaining in epithelial cells only and 13 (22%) cases strong stain in endometrial stromal cells and weak or absence stain in epithelial cells. Six (66.7%) cases of papillary serous carcinomas and one case of MMMT have been found strongly positive for leptin immunostaining in endometrial stromal cells and epithelial cells (**Figure 1**). The only case of clear cell carcinoma in this study showed positive immunostaining in epithelial cells (**Table 1**). There was considerable heterogeneity of leptin immunostaining between endometrial tumors in respect of the number of positively stained cells and pattern of staining. For example, some cases showed apical cytoplasmic staining, some cases showed staining in the whole cytoplasm, and other cases showed perinuclear staining. In addition, the immunostaining was selective for certain tumor glands and cells in some cases.

Twenty-one control cases (11 proliferative endometrium, 8 cases of secretory, and 2 polyps) representing 70% of the control group showed strong immunostaining. No statistical difference in leptin expression was observed between tumor cases and control group.

Histotype of an endometrial tumor has been found to be significantly associated with the pattern of leptin expression (*P*-value = 0.005), i.e., a large proportion of endometrioid adenocarcinomas is associated with leptin immunostaining when it is expressed in epithelial cells only while the large proportion of serous carcinoma is associated with leptin immunoreactivity in endometrial stromal cells. Tumor stage is also significantly associated with cell type leptin immunostaining (*P*-value = 0.007), a considerable fraction of stage II is higher in epithelial leptin immunostaining whereas leptin immunoreactivity in endometrial stromal cells is more frequent in stage III (**Table 1**). Disease recurrence rate is significantly higher in patients whom endometrial stromal cells are positive for leptin immunostaining (*P*-value = 0.000). Poor survival status (death) is also significantly associated with a group of patients whom endometrial stromal cells showed positive leptin immunoreactivity (*P*-value = 0.000) (**Table 1**). The

result of log-rank (Mantel-Cox) test for equality of survival distributions for the different pattern of leptin immunostaining showed significant different survival distribution (*P*-Value = 0.002). **Figure 2** shows significantly poor survival behavior with leptin immunostaining in endometrial stromal cells so it can be said that leptin immunostaining in endometrial stromal cells is positively related to poor survival.

Discussion

In Saudi Arabia, malignant neoplasms of endometrium rated sixth amongst the female population in 2010. The most common type is endometrial endometrioid adenocarcinoma accounting for more than 70%, and less frequently, serous carcinoma, clear cell adenocarcinoma, endometrial stromal sarcoma, adenocarcinoma with mixed subtypes, and others [Cancer Incidence Report Saudi Arabia 2012, Saudi Cancer Registry. http://www.chs.gov.sa/Ar/Health-Records/CancerRegistry/Pages/Cancer Registry Records. asp]. A vigorous marker that differentiates between these histological types of endometrial carcinomas is probably to be valuable and helpful in deciding the best management plan. Therefore, the current paper investigated the expression phenotype of leptin in endometrial carcinomas and its diagnostic and prognostic capacities in endometrial malignancies of the tested Saudi female population.

Many studies have implicated leptin phenotype in various steps of malignancy such as cell proliferation, migration, invasion, metastasis, recurrence and treatment response in several organs including liver [14], lung [24], stomach [17], thyroid [25], breast [16], colon [26], larynx [27], and esophagus [28]. In respect of the role of leptin in the development and progression of endometrial carcinoma, many studies demonstrated a direct role for leptin in endometrial cancer growth and invasion [11, 13, 18, 29-31]. Even more, several studies reported evidence that high serum level of leptin is associated with increased risk of endometrial cancer and is considered an independent risk factor [22, 32, 33].

In the present study, the frequency of leptin expression of the 30 controls (70%), which was observed only in the cytoplasm of glandular epithelium, is in accordance with the findings of Koda and colleagues [34] who reported positive leptin immunostaining in 68% of normal endometrium, and Ozler and associates [35] who found positive leptin expression in different phases of the human endometrium by using immunohistochemistry staining. In respect of endometrial carcinomas in this study, leptin immunoreactivity was similarly frequent in carcinomas (67%) compared with noncancerous endometrium. However, our results are in line with those of Wincewicz and coworkers [36] and Koda and colleagues [34], who found positive leptin immunostaining in 60% and 56.7% of endometrial carcinomas respectively.

The present study is the first to report that the pattern of leptin expression is significantly associated with histotype, stage, recurrence and poor outcomes (death) of endometrial carcinomas, whereas other studies did not find similar association in endometrial carcinomas [34, 36]. However, our findings are consistent with many other studies which have reported that leptin expression was associated with one or more of the clinicopathological parameters such as higher clinical stage, invasion, metastasis, recurrence, chemo-resistance and poor prognostic outcomes in laryngeal squamous cell carcinoma [27], esophageal squamous cell carcinoma [28], gastric cancer [37], non-small-cell lung cancer [24], and papillary thyroid carcinoma [25].

The variations between the present study and previous studies could be explained by procedures sensitivity, populations' diversity, cell type leptin expression and variances in sample size. The current study and other related reports which made an effort to assess the diagnostic and prognostic use of leptin immunostaining in endometrial carcinomas had few limitations such as the comparatively small sample size involved in these studies and the semi-quantitative interpretation of immunostaining. However, greater inclusive studies are undoubtedly of great value for estimating the diagnostic and prognostic values of leptin immunostaining in endometrial malignancy.

The results of our study confirm the diagnostic and prognostic values of leptin in supporting the diagnosis and prognosis of endometrial carcinomas. These preliminary findings recommend that leptin may be a valuable marker for predicting histotype, stage, recurrence and

poor prognosis in endometrial carcinoma. The correlation of leptin with several clinicopathological parameters suggests the involvement of this molecule in endometrial tumor progression.

Acknowledgements

This project was funded by the Deanship of Scientific Research, (DSR), King Abdulaziz University (KAU), Jeddah, under grant number (426/140/1437). The authors acknowledge with thanks DSR technical and financial support.

Disclosure of conflict of interest

None.

Address correspondence to: Jaudah Al-Maghrabi, Department of Pathology, King Abdulaziz University, P.O. Box 80205, Jeddah 21589, Saudi Arabia. Tel: +96612 6401000 Ext. 17069; Fax: +966 2 6401000 Ext. 17223; E-mail: jalmaghrabi@hotmail.com; jalmgrabi@kau.edu.sa

References

[1] Siegel R, Ma J, Zou Z and Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[2] Fadare O, Zheng W, Crispens MA, Jones HW, Khabele D, Gwin K, Liang SX, Mohammed K, Desouki MM, Parkash V and Hecht JL. Morphologic and other clinicopathologic features of endometrial clear cell carcinoma: a comprehensive analysis of 50 rigorously classified cases. Am J Cancer Res 2013; 3: 70-95.

[3] Soslow RA, Bissonnette JP, Wilton A, Ferguson SE, Alektiar KM, Duska LR and Oliva E. Clinicopathologic analysis of 187 high-grade endometrial carcinomas of different histologic subtypes: similar outcomes belie distinctive biologic differences. Am J Surg Pathol 2007; 31: 979-987.

[4] Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, Powell MA, Hendrickson MR, Kapp DS and Chan JK. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer 2006; 94: 642-646.

[5] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L and Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425-432.

[6] Baratta M. Leptin--from a signal of adiposity to a hormonal mediator in peripheral tissues. Med Sci Monit 2002; 8: RA282-292.

[7] Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y and Lewin MJ. The stomach is a source of leptin. Nature 1998; 394: 790-793.

[8] Caro JF, Sinha MK, Kolaczynski JW, Zhang PL and Considine RV. Leptin: the tale of an obesity gene. Diabetes 1996; 45: 1455-1462.

[9] Gonzalez RR, Simon C, Caballero-Campo P, Norman R, Chardonnens D, Devoto L and Bischof P. Leptin and reproduction. Hum Reprod Update 2000; 6: 290-300.

[10] Carino C, Olawaiye AB, Cherfils S, Serikawa T, Lynch MP, Rueda BR and Gonzalez RR. Leptin regulation of proangiogenic molecules in benign and cancerous endometrial cells. Int J Cancer 2008; 123: 2782-2790.

[11] Gao J, Tian J, Lv Y, Shi F, Kong F, Shi H and Zhao L. Leptin induces functional activation of cyclooxygenase-2 through JAK2/STAT3, MAPK/ERK, and PI3K/AKT pathways in human endometrial cancer cells. Cancer Sci 2009; 100: 389-395.

[12] Sierra-Honigmann MR, Nath AK, Murakami C, Garcia-Cardena G, Papapetropoulos A, Sessa WC, Madge LA, Schechner JS, Schwabb MB, Polverini PJ and Flores-Riveros JR. Biological action of leptin as an angiogenic factor. Science 1998; 281: 1683-1686.

[13] Sharma D, Saxena NK, Vertino PM and Anania FA. Leptin promotes the proliferative response and invasiveness in human endometrial cancer cells by activating multiple signal-transduction pathways. Endocr Relat Cancer 2006; 13: 629-640.

[14] Saxena NK, Sharma D, Ding X, Lin S, Marra F, Merlin D and Anania FA. Concomitant activation of the JAK/STAT, PI3K/AKT, and ERK signaling is involved in leptin-mediated promotion of invasion and migration of hepatocellular carcinoma cells. Cancer Res 2007; 67: 2497-2507.

[15] Bartucci M, Svensson S, Ricci-Vitiani L, Dattilo R, Biffoni M, Signore M, Ferla R, De Maria R and Surmacz E. Obesity hormone leptin induces growth and interferes with the cytotoxic effects of 5-fluorouracil in colorectal tumor stem cells. Endocr Relat Cancer 2010; 17: 823-833.

[16] Dubois V, Jarde T, Delort L, Billard H, Bernard-Gallon D, Berger E, Geloen A, Vasson MP and Caldefie-Chezet F. Leptin induces a proliferative response in breast cancer cells but not in normal breast cells. Nutr Cancer 2014; 66: 645-655.

[17] Lee KN, Choi HS, Yang SY, Park HK, Lee YY, Lee OY, Yoon BC, Hahm JS and Paik SS. The role of leptin in gastric cancer: clinicopathologic features and molecular mechanisms. Biochem Biophys Res Commun 2014; 446: 822-829.

[18] Zhou X, Li H, Chai Y and Liu Z. Leptin inhibits the apoptosis of endometrial carcinoma cells through activation of the nuclear factor kappaB-inducing kinase/ikappaB kinase pathway. Int J Gynecol Cancer 2015; 25: 770-778.
[19] Ogunwobi OO and Beales IL. Cyclo-oxygenase-independent inhibition of apoptosis and stimulation of proliferation by leptin in human colon cancer cells. Dig Dis Sci 2007; 52: 1934-1945.
[20] Ando S and Catalano S. The multifactorial role of leptin in driving the breast cancer microenvironment. Nat Rev Endocrinol 2012; 8: 263-275.
[21] Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, Kim SY, Hamnvik OP and Koniaris A. Leptin in human physiology and pathophysiology. Am J Physiol Endocrinol Metab 2011; 301: E567-584.
[22] Luhn P, Dallal CM, Weiss JM, Black A, Huang WY, Lacey JV Jr, Hayes RB, Stanczyk FZ, Wentzensen N and Brinton LA. Circulating adipokine levels and endometrial cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev 2013; 22: 1304-1312.
[23] Al-Maghrabi J, Emam E, Gomaa W, Saggaf M, Buhmeida A, Al-Qahtani M and Al-Ahwal M. c-MET immunostaining in colorectal carcinoma is associated with local disease recurrence. BMC Cancer 2015; 15: 676.
[24] Xu YJ, Shao YF, Zhao X, Geng YT, Wang K and Yin YM. Expression and clinical significance of leptin, the functional receptor of leptin (OB-Rb) and HER-2 in non-small-cell lung cancer: a retrospective analysis. J Cancer Res Clin Oncol 2011; 137: 1841-1848.
[25] Fan YL and Li XQ. Expression of leptin and its receptor in thyroid carcinoma: distinctive prognostic significance in different subtypes. Clin Endocrinol (Oxf) 2015; 83: 261-267.
[26] Jeong WK, Baek SK, Kim MK, Kwon SY and Kim HS. Prognostic significance of tissue leptin expression in colorectal cancer patients. Ann Coloproctol 2015; 31: 222-227.
[27] Gallina S, Sireci F, Lorusso F, DI Benedetto DV, Speciale R, Marchese D, Costantino C, Napoli G, Tessitore V, Cucco D, Leone A, Bonaventura G, Uzzo ML, Spatola GF. The immunohistochemical peptidergic expression of leptin is associated with recurrence of malignancy in laryngeal squamous cell carcinoma. Acta Otorhinolaryngol Ital 2015; 35: 15-22.
[28] Duan X, Tang P, Zhang H and Yu Z. [Expression of leptin and adiponectin in esophageal squamous cell carcinoma and their clinical significance]. Zhonghua Zhong Liu Za Zhi 2014; 36: 839-843.
[29] Catalano S, Giordano C, Rizza P, Gu G, Barone I, Bonofiglio D, Giordano F, Malivindi R, Gaccione D, Lanzino M, De Amicis F and Ando S. Evidence that leptin through STAT and CREB signaling enhances cyclin D1 expression and promotes human endometrial cancer proliferation. J Cell Physiol 2009; 218: 490-500.
[30] Liu Y, Lv L, Xiao W, Gong C, Yin J, Wang D and Sheng H. Leptin activates STAT3 and ERK1/2 pathways and induces endometrial cancer cell proliferation. J Huazhong Univ Sci Technolog Med Sci 2011; 31: 365-370.
[31] Liu L, Wang L, Zheng J and Tang G. Leptin promotes human endometrial carcinoma cell proliferation by enhancing aromatase (P450arom) expression and estradiol formation. Eur J Obstet Gynecol Reprod Biol 2013; 170: 198-201.
[32] Ma Y, Liu Z, Zhang Y and Lu B. Serum leptin, adiponectin and endometrial cancer risk in Chinese women. J Gynecol Oncol 2013; 24: 336-341.
[33] Wang PP, He XY, Wang R, Wang Z and Wang YG. High leptin level is an independent risk factor of endometrial cancer: a meta-analysis. Cell Physiol Biochem 2014; 34: 1477-1484.
[34] Koda M, Sulkowska M, Wincewicz A, Kanczuga-Koda L, Musiatowicz B, Szymanska M and Sulkowski S. Expression of leptin, leptin receptor, and hypoxia-inducible factor 1 alpha in human endometrial cancer. Ann N Y Acad Sci 2007; 1095: 90-98.
[35] Ozler A, Kuscu NK, Temiz P, Kandiloglu AR and Koyuncu FM. Leptin expression in proliferative, secretory and hyperplastic endometrial tissues. J Turk Ger Gynecol Assoc 2011; 12: 157-161.
[36] Wincewicz A, Koda M, Sulkowska M, Kanczuga-Koda L and Sulkowski S. Comparison of STAT3 with HIF-1alpha, Ob and ObR expressions in human endometrioid adenocarcinomas. Tissue Cell 2008; 40: 405-410.
[37] Bain GH, Collie-Duguid E, Murray GI, Gilbert FJ, Denison A, McKiddie F, Ahearn T, Fleming I, Leeds J, Phull P, Park K, Nanthakumaran S, Grabsch HI, Tan P, Welch A, Schweiger L, Dahle-Smith A, Urquhart G, Finegan M, Matula KM and Petty RD. Tumour expression of leptin is associated with chemotherapy resistance and therapy-independent prognosis in gastro-oesophageal adenocarcinomas. Br J Cancer 2014; 110: 1525-1534.