European Review for Medical and Pharmacological Sciences 2018; 22: 6294-6299

Biomolecular basis related to inflammation in the pathogenesis of endometrial cancer

C. BORGHI[1], U. INDRACCOLO[1], G. SCUTIERO[1], P. IANNONE[1], R. MARTINELLO[1], P. GRECO[1], F. GRECO[2], L. NAPPI[2]

[1]Department of Morphology, Surgery and Experimental Medicine, Section of Obstetrics and Gynecology, University of Ferrara, Ferrara, Italy
[2]Department of Medical and Surgical Sciences, Institute of Obstetrics and Gynecology, University of Foggia, Foggia, Italy

Abstract. – OBJECTIVE: Endometrial cancer (EC) is a complex gynecological neoplasm with several clinical, histopathological and genetic features. Different hormonal, metabolic and biochemical axes are involved in pathogenesis. Obesity is a well-known risk factor for this disease and the role of local and systemic effects of adipose tissue, especially in the promotion of subclinical chronic inflammation, is an important issue. Indeed, inflammation is related to the pathogenesis of different tumors, including EC. This review aims to remark the role of obesity and inflammation in the pathogenesis of EC cancer through an exploration of the current literature.

MATERIALS AND METHODS: We performed a comprehensive review of the literature through a PubMed search using key words and including English language papers looking at this topic.

RESULTS: Only few authors analyzed the role of inflammatory cytokines released by adipose tissue in visceral abdominal fat depots. Tumor Necrosis Factor-α, Interleukin-6, Interleukin-1 Receptor Antagonist, Nuclear Factor-kB, Leptin, Adiponectin and C Reactive Protein were studied for cancer risk prediction models, risk stratification or targeted therapies. Furthermore, genetic studies evaluated the effect of inflammatory cytokines secreted by visceral adipocytes in the modulation of angiogenesis and signaling pathways such as PI3K/AKT/mTOR, that result altered in the pathogenesis of EC.

CONCLUSIONS: The identification of inflammatory biomarkers released by adipose tissue, in the pathogenesis of EC, could be useful in improving diagnostic accuracy, identifying targets of therapy, suggesting useful lifestyle behaviors. A deeper knowledge of the genetic background of alterations in inflammatory pathway genes could better define the population exposed to a higher susceptibility to EC due to genetic polymorphisms. Future studies are needed to better understand this field.

Key Words:
Endometrial Cancer, Inflammation, Cytokines, Obesity.

Introduction

Endometrial cancer (EC) is the most common female genital tract malignancy in industrialized countries and the second most common in developing countries. It counts 140 000 new cases every year worldwide, about 6% of new cancer cases and 3% of cancer death per year[1,2]. Historically, EC has been classified on the basis of clinical, endocrine and epidemiological characteristics into Type I (80-90%) and Type II (10-20% of cases). Histopathological classification further divided tumors into endometrioid and non-endometrioid[3,4]. Nevertheless, all these classifications didn't take into account the complexity of this disease. Recently, the mapping of genomic landscape of ECs by the Cancer Genome Atlas Research Network has enriched the knowledge of this kind of neoplasia, underlying the great molecular heterogeneity and defining four molecular subgroups: (1) POLE ultramutated; (2) MSI-hypermutated; (3) copy number low; (4) copy number high[5-8]. These differences are fundamental to better understand the endometrial tumorigenesis and to predict its variable prognosis and sensitivity to treatment[7,9]. Among the proven risk factors for endometrial neoplasia, those related to an excess of estrogens and typical clinical features recur. High Body Mass Index (BMI), metabolic syndrome, hypertension, type 2 diabetes mellitus, hypertriglyceridaemia, nulliparity, infertility, polycystic ovarian syndrome, early menarche, late menopause, unopposed estrogen therapy are the most common examples[3,10]. All these conditions are characterized by an excess of biologically available estrogen or an excess of estrogen related to progesterone. After menopause, adipose tissue represents the primary source of estrogen, whose

Corresponding Author: Chiara Borghi, MD; e-mail: borghi.chr@gmail.com

levels correlates with elevated BMI[11]. Although these factors are linked to endometrioid EC, their impact on clinical and histological phenotype is poorly understood and several ongoing studies are aimed to clarify molecular mechanisms connected to its genesis. Furthermore, a number of other hormonal, metabolic and biochemical axes have been associated with the risk. In the huge field of these observations, obesity and inflammation have been hypothesized to play a role in EC development, either by mediating estrogens action and as independent factors[12,13]. This review is aimed to remark the role of obesity and inflammation in the pathogenesis of EC through an exploration of the current literature

Materials and Methods

We performed a comprehensive review of the literature through a PubMed search using the key terms "endometrial cancer", "inflammation", "cytokines", "obesity". We then surveyed the English language literature for studies looking at this topic. The authors identified the most relevant studies through the selection of abstracts, including systematic reviews, studies with the longest follow-up, and studies discussing molecular basis and pathophysiology of the studied disease. The search yielded a total of 44 papers, which were reviewed by the authors.

Results

Obesity, Inflammation and Cancer

The role of inflammation in cancer development is well known. Inflammatory pathways influencing tumorigenesis can be intrinsic or extrinsic. The first is sustained by genetic mutations able to initiate cancer transformation and further up-regulate the expression of inflammatory mediators. The second is related to a chronic inflammatory condition leading to the initiation of cancer and further production of inflammatory mediators[14]. Even if genetic mutations seem to be the most important initiating factor, contribution to tumor initiation and growth is really complex and several elements influence it. Among them, obesity represents a key predisposing condition[15]. Obesity, defined as excess in adipose tissue, with its increasing incidence, represents a challenge to global health. Adipose tissue is a complex heterogeneous organ acting in the metabolic homeostasis of the organism through the interaction of many different cell types, such as adipocytes, pre-adipocytes, macrophages, endothelial cells and many immune cells. It is already clear that obesity is associated with an increased frequency of many types of cancer, but the relative roles of the different cells and the molecular pathways involved in carcinogenesis are still unclear[15]. The hypertrophied adipose tissue secretes a large amount of factors such as leptin, hepatocyte growth factor, angioprotein 1, Vascular Endothelial Growth Factor (VEGF) and many others. All of them are crucial for communication among different cell types and tissue growth[16]. Some of these factors, such as adipokines derived from adipocytes, are associated with the inflammatory system. The most studied, because of their relation with cancer risk, are leptin, a potent inflammatory agent, and adiponectin, with anti-inflammatory activity[17]. The cytokines secreted by adipose tissue can activate macrophages or other inflammatory cells, and promote cancer[16]. It has already been defined that macrophage infiltration has an important role in tumor microenvironment and contributes to tissue invasion, angiogenesis and metastasis[18]. In summary, a large body of literature demonstrates that a combination of factors secreted by adipocytes, such as increased leptin, decreased adiponectin and increased inflammatory cytokines secretion (Tumor Necrosis Factor, Interleukin 6 and others), in addition to secondary effects of obesity, i.e. hyperinsulinemia and hyperlipidemia, results in a higher risk of developing different types of neoplasms, such as breast, bladder, stomach, blood, colon and liver cancer[14,19]. It's not easy to assess which is more important in increasing the likelihood of carcinogenesis, whether adipose tissue itself or consequences of obesity; several ongoing studies are aimed to explore the different roles[15]. Insights about the complex biology of adipose tissue have defined a new classification based on the risk of metabolic complications of obesity. This divides Metabolically Healthy Obesity (MHO) from Metabolically Unhealthy Obesity (MUO), with differences in terms of body fat distribution[20,21]. Furthermore, it is proven that ectopic fat tissue depots surrounding organs and blood vessels, mostly prevalent in MUO, have several local and systemic effects promoting subclinical chronic inflammation. This is due to the infiltration of adipose tissue by macrophages and to the deregulation of cytokines and secreting growth factors[22]. All these conditions are already

considered as proven risk factors for cardiovascular diseases and may contribute to several other pathologies, including implications in cancer epidemiology[17,20].

Obesity, Inflammation and Endometrial Cancer

Evidence supporting the critical role of inflammation in initiation, promotion, malignant degeneration, invasion and metastasis has been confirmed in the pathogenesis of different neoplasms. Less is still known about EC, the most common gynecological malignancy[23,24]. Obesity is an important independent risk factor for both type 1 and type 2 EC. Nevertheless, the metabolic, immunogenic and inflammatory environment regulating the underlying biological relation between obesity and the different subsets of this neoplasia are still poorly understood. High visceral abdominal fat exerts an independent metabolic and endocrine activity, different from that of subcutaneous fat tissue. It is thought to promote carcinogenesis by inducing a state of low-grade chronic inflammation and is considered relevant in terms of pathogenic and prognostic value[18]. Since adipose tissue and uterus are highly vascularized and interconnected through blood vessels, growth factors secreted by adipocytes can easily alter uterine physiology. The differences in terms of molecular pathways such as KRAS activation and inflammation in the pathogenesis of endometrioid EC and its precursors in obese patients seem to be different if compared to non-obese women[11]. Few studies tried to improve the knowledge of this complex interaction of elements and the involved mechanisms. Modugno et al[13] in 2005 first hypothesized a relation between a chronic inflammation state and endometrial cellular division, higher risk for replication errors and ineffective DNA repair. They put in evidence that an inflammatory milieu in endometrial tissue with the release of cytokines and growth factors was related to initiation and promotion of EC. Furthermore, they underlined that all the known risk factors for neoplasia were directly related to inflammation or were indirectly involved in modulation of the inflammatory pathway. For example, unopposed estrogen action was related to increased pro-inflammatory response in the endometrium. Obesity, diabetes mellitus, polycystic ovarian syndrome were associated to an increased pro-inflammatory milieu. Early menarche, late menopause and menorrhagia were associated to increased exposure to inflammation due to longer menstruation[13]. Among all the known pro-inflammatory cytokines, Tumor Necrosis Factor-α (TNF-α) is one of the most powerful. Its relationship with EC has been analyzed in a case-control study by Dossus et al[26] in 2011, with data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort[27]. They analyzed serum TNF-α and plasma TNF soluble receptors (sTNFR1 and sTNFR2). The results from 270 cases and 518 controls, showed a positive association of TNF-α and sTNFRs with endometrial proliferation and angiogenesis promotion. As a matter of fact, TNF-α was related to known risk factors for EC, such as enhanced local estrogen synthesis, increased development of insulin resistance and type 2 diabetes mellitus. Researches could not exclude that the presence of a tumor itself could enhance the levels of circulating inflammatory mediators, but results supporting the role of TNF-α and its receptors were of particular interest in terms of therapeutic possibilities with TNF-α inhibitors[26]. The same group further analyzed the role of circulating cytokines and acute phase reactants in the pathogenesis of EC[28]. A case-control study, nested within the EPIC study[27], aimed to investigate the association of C-Reactive Protein (CRP), Interleukin-6 (IL6) and IL1Ra with EC risk and to what extent these factors can relate obesity and EC. Blood samples from 305 cases taken prospectively prior to EC diagnosis, who were incidentally found with disease during follow up, and 574 healthy controls were analyzed. In conclusion, high blood concentrations of cytokines were significantly associated with EC risk and their association was largely dependent on the levels of patients' adiposity, thus indicating modulators of aromatase activity of cytokines within the adipose tissue[28]. Another investigation within the data of the EPIC cohort[27] included 233 cases and 446 controls. Dossus et al[12] analyzed a large set of serum biomarkers, taken from pre-diagnostic blood samples, including hormones, growth factors and cytokines, in order to examine their association with EC. This analysis confirmed that TNF-α and sTNFRs, along with IL-6 and CRP, were inflammatory factors associated with an increased risk of EC in post-menopausal women. Dossus et al[12] concluded underlying the complex interrelation of all the physiological pathways related to EC pathogenesis, including insulin resistance/metabolic syndrome, steroids and finally inflammation. Trabert et al[29] in 2016 in a nested

case-control study within the PLCO Screening Trial measured blood level of 64 inflammatory biomarkers in 284 cases of endometrial cancer and 284 controls. They found a higher risk for endometrial cancer among obese women with the highest inflammation scores and several inflammation markers, such as adipokines, inflammatory cytokines, angiogenic factors and acute phase proteins. Only VEGF-A was recognized as a risk factor independent of BMI. Sahoo et al[16] investigated the effect of cytokines secreted by adipose tissue and, in particular, visceral adipocytes in the modulation and stimulation of angiogenesis and EC proliferation through the action of VEGF. They confirmed that VEGF stimulates the PI3K/AKT/mTOR signaling pathway, a regulator of cellular growth and survival, the most frequently altered pathway in EC. Their results indicate that VEGF expression is directly linked to BMI: the large amount of visceral adipose tissue in obese women is linked to up-regulated VEGF signaling, resulting in more tumor vascularization and higher mTOR activity in the promotion of EC. These results have an increasing interest in terms of pathways-targeted therapies, since mTOR and VEGF inhibitors treatments could be a promising option to reduce the occurrence of EC in obese women[16]. Biomarkers related to EC risk including steroid hormones, factors linked to metabolic syndrome, insulin resistance and inflammation can be found in visceral abdominal fat depots. Their recognition in peripheral serum as a potential tool for cancer risk prediction models is interesting in risk stratification. This setting has been studied with un-univocal results, since Fortner et al[30] achieved only a modest improvement in identification of pattern of high-risk patients. More research[30-33] is needed to recognize hormones, etiologic markers and confirmed genetic markers useful in improving discrimination of patients.

Conclusions

The aim of this study was to review the current knowledge about the complex mechanisms underlying the pathogenesis of EC, related to well known risk factors such as obesity and pro-inflammatory conditions. The identification of the involved biomarkers could be useful in improving diagnostic accuracy and identifying targets of therapy, defining systemic treatment strategies and suggesting useful lifestyle behaviors[34-37]. A deeper understanding of the genetic background of alterations in inflammatory pathway genes could better define populations exposed to a higher susceptibility to EC due to genetic polymorphisms[38-42]. Furthermore, a better understanding of these molecular pathways could be useful for those patients who could take advantage of conservative treatments such as women with endometrial atypical hyperplasia who want to preserve fertility or to those with EC who are inoperable[43,44].

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Jemal A, Bray F, Ferlay J, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
2) Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2018. CA Cancer J Clin 2018; 68: 7-30.
3) Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, Sessa C, the ESMO–ESGO–ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Int J Gynecol Cancer 2016; 26: 2-30.
4) International Agency for Research on Cancer (IARC). WHO Classification of Tumours of Female Reproductive Organs 4th Edition. International Agency for Research on Cancer, 2014.
5) Hussein YR, Weigelt B, Levine DA, Schoolmeester JK, Dao LN, Balzer BL, Liles G, Karlan B, Köbel M, Lee CH, Soslow RA. Clinicopathological analysis of endometrial carcinomas harboring somatic POLE exonuclease domain mutations. Mod Pathol 2015; 28: 505-514.
6) Gargiulo P, Della Pepa C, Berardi S, Califano D, Scala S, Buonaguro L, Ciliberto G, Brauchli P, Pignata S. Tumor genotype and immune microenvironment in POLE-ultramutated and MSI-hypermutated endometrial cancers: new candidates for checkpoint blockade immunotherapy? Cancer Treat Rev 2016; 48: 61-68.
7) Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol 2014; 15: 268-278.
8) The Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature 2013; 497: 67-73.
9) Berstein LM. Renovated (nondual) approach to endometrial cancer typing: endocrine and inflammatory issues. Future Oncol 2017; 13: 109-112.
10) Schindler AE. Progestogen deficiency and endome-

trial cancer risk. Maturitas 2009; 62: 334-337.

11) Berg A, Hoivik EA, Mjøs S, Holst F, Werner HMJ, Tangen IL, Taylor-Weiner A, Gibson WJ, Kusonmano K, Wik E, Trovik J, Halle MK, Øyan AM, Kalland KH, Cherniack AD, Beroukhim R, Stefansson I, Mills GB, Krakstad C, Salvesen HB. Molecular profiling of endometrial carcinoma precursor, primary and metastatic lesions suggests different targets for treatment in obese compared to non-obese patients. Oncotarget 2014; 6: 1327-1339.

12) Dossus L, Lukanova A, Rinaldi S, Allen N, Cust AE, Becker S, Tjonneland A, Hansen L, Overvad K, Chabbert-Buffet N, Mesrine S, Clavel-Chapelon F, Teucher B, Chang-Claude J, Boeing H, Drogan D, Trichopoulou A, Benetou V, Bamia C, Palli D, Agnoli C, Galasso R, Tumino R, Sacerdote C, Bueno-de-Mesquita HB, van Duijnhoven FJB, Peeters PHM, Onland-Moret NC, Redondo ML, Travier N, Sanchez MJ, Altzibar JM, Chirlaque MD, Barricarte A, Lundin E, Khaw KT, Wareham N, Fedirko V, Romieu I, Romaguera D, Norat T, Riboli E, Kaaks R. Hormonal, metabolic, and inflammatory profiles and endometrial cancer risk within the EPIC cohort – a factor analysis. Am J Epidemiol 2013; 177: 787-799.

13) Modugno F, Ness RB, Chen C, Weiss NS. Inflammation and endometrial cancer: a hypothesis. Cancer Epidemiol Biomarkers Prev 2005; 14: 2840-2848.

14) Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010; 140: 883-899.

15) Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 2011; 11: 886-895.

16) Sahoo SS, Lombard JM, Ius Y, O'Sullivan R, Wood LG, Nahar P, Jaaback K, Tanwar PS. Adipose-derived VEGF-mTOR signaling promotes endometrial hyperplasia and cancer: implications for obese women. Mol Cancer Res 2018; 16: 309-321.

17) Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer 2015; 15: 484-498.

18) Pollard J. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer 2004; 4: 71-78.

19) Cignarelli A, Genchi VA, Caruso I, Natalicchio A, Perrini S, Laviola L, Giorgino F. Diabetes and cancer: pathophysiological fundamentals of a 'dangerous affair'. Diabetes Res Clin Pract 2018 Apr 19. pii: S0168-8227(18)30359-0. doi: 10.1016/j.diabres.2018.04.002. [Epub ahead of print]

20) Moore LL, Chadid S, Singer MR, Kreger BE, Denis GV. Metabolic health reduces risk of obesity-related cancer in framingham study adults. Cancer Epidemiol Biomarkers Prev 2014; 23: 2057-2065.

21) Stefan N, Häring H, Hu F, Schulze M. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol 2013; 1: 152-162.

22) Stienstra R, van Diepen JA, Tack CJ, Zaki MH, van de Veerdonk FL, Perera D, Neale GA, Hooiveld GJ, Hijmans A, Vroegrijk I, van den Berg S, Romijn J, Rensen PC, Joosten LA, Netea MG, Kanneganti TD. Inflammasome is a central player in the induction of obesity and insulin resistance. Proc Natl Acad Sci U S A 2011; 108: 15324-15329.

23) Sanderson PA, Critchley HOD, Williams ARW, Arends MJ, Saunders PT. New concepts for an old problem: the diagnosis of endometrial hyperplasia. Hum Reprod Update 2017; 23: 232-254.

24) Wallace AE, Gibson DA, Saunders PTK, Jabbour HN. Inflammatory events in endometrial adenocarcinoma. J Endocrinol 2010; 206: 141-157.

25) Mauland KK, Eng Ø, Ytre-Hauge S, Tangen IL, Berg A, Salvesen HB, Salvesen ØO, Krakstad C, Trovik J, Hoivik EA, Werner HMJ, Mellgren G, Haldorsen IS. High visceral fat percentage is associated with poor outcome in endometrial cancer. Oncotarget 2017; 8: 105184-105195.

26) Dossus L, Becker S, Rinaldi S, Lukanova A, Tjønneland A, Olsen A, Overvad K, Chabbert-Buffet N, Boutron-Ruault MC, Clavel-Chapelon F, Teucher B, Chang-Claude J, Pischon T, Boeing H, Trichopoulou A, Benetou V, Valanou E, Palli D, Sieri S, Tumino R, Sacerdote C, Galasso R, Redondo ML, Bonet CB, Molina-Montes E, Altzibar JM, Chirlaque MD, Ardanaz E, Bueno-de-Mesquita HB, van Duijnhoven FJ, Peeters PH, Onland-Moret NC, Lundin E, Idahl A, Khaw KT, Wareham N, Allen N, Romieu I, Fedirko V, Hainaut P, Romaguera D, Norat T, Riboli E, Kaaks R. Tumor necrosis factor (TNF)-a, soluble TNF receptors and endometrial cancer risk: the EPIC study. Int J Cancer 2011; 129: 2032-2037.

27) Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondière UR, Hémon B, Casagrande C, Vignat J, Overvad K, Tjønneland A, Clavel-Chapelon F, Thiébaut A, Wahrendorf J, Boeing H, Trichopoulos D, Trichopoulou A, Vineis P, Palli D, Bueno-De-Mesquita HB, Peeters PH, Lund E, Engeset D, González CA, Barricarte A, Berglund G, Hallmans G, Day NE, Key TJ, Kaaks R, Saracci R. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002; 5: 1113-1124.

28) Dossus L, Rinaldi S, Becker S, Lukanova A, Tjonneland A, Olsen A, Stegger J, Overvad K, Chabbert-Buffet N, Jimenez-Corona A, Clavel-Chapelon F, Rohrmann S, Teucher B, Boeing H, Schütze M, Trichopoulou A, Benetou V, Lagiou P, Palli D, Berrino F, Panico S, Tumino R, Sacerdote C, Redondo ML, Travier N, Sanchez MJ, Altzibar JM, Chirlaque MD, Ardanaz E, Bueno-de-Mesquita HB, van Duijnhoven FJ, Onland-Moret NC, Peeters PH, Hallmans G, Lundin E, Khaw KT, Wareham N, Allen N, Key TJ, Slimani N, Hainaut P, Romaguera D, Norat T, Riboli E, Kaaks R. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case – control study. Endocr Relat Cancer 2010; 17: 1007-1019.

29) Trabert B, Eldridge RC, Pfeiffer RM, Shiels MS, Kemp TJ, Guillemette C, Hartge P, Sherman ME, Brinton LA, Black A, Chaturvedi AK, Hildesheim A, Berndt SI, Safaeian M, Pinto L, Wentzensen N. Prediagnostic

circulating inflammation markers and endometrial cancer risk in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. Int J Cancer 2017; 140: 600-610.

30) Fortner RT, Hüsing A, Kühn T, Konar M, Overvad K, Tjønneland A, Hansen L, Boutron-Ruault MC, Severi G,Fournier A, Boeing H, Trichopoulou A, Benetou V, Orfanos P, Masala G, Agnoli C, Mattiello A, Tumino R, Sacerdote C, Bueno-de-Mesquita HB, Peeters PH, Weiderpass E, Gram IT, Gavrilyuk O, Quirós JR, Maria Huerta J, Ardanaz E, Larrañaga N, Lujan-Barroso L, Sánchez-Cantalejo E, Butt ST, Borgquist S, Idahl A, Lundin E, Khaw KT, Allen NE, Rinaldi S, Dossus L, Gunter M, Merritt MA, Tzoulaki I, Riboli E, Kaaks R. Endometrial cancer risk prediction including serum-based biomarkers: results from the EPIC cohort. Int J Cancer 2017; 140: 1317-1323.

31) Slomovitz BM, Coleman RL. The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. Clin Cancer Res 2012; 18: 5856-5864.

32) Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell 2017; 169: 361-371.

33) Bajwa P, Sahoo SS, Tanwar PS. Age-related mTOR in gynaecological cancers. Aging 2017; 9: 301-302.

34) Brasky TM, Rodabough RJ, Liu J, Kurta ML, Wise LA, Orchard TS, Cohn DE, Belury MA, White E, Manson JE, Neuhouser ML. Long-chain ω-3 fatty acid intake and endometrial cancer risk in the women's health initiative. Am J Clin Nutr 2015; 101: 824-834.

35) World Cancer Research Fund / American Institute for Cancer Research. Continuous cer. 2013. Available at http://www.dietandcancerreport.org.

36) Gibson DA, Saunders PTK. Endocrine disruption of oestrogen action and female reproductive tract cancers. Endocr Relat Cancer 2014; 21: T13-T31.

37) Moore EE, Danielewski JA, Garland SM, Tan J, Quinn MA, Stevens MP, Tabrizi SN. Clearance of human papillomavirus in women treated for cervical dysplasia. Obstet Gynecol 2011; 117: 101-108.

38) Delahanty RJ, Xiang YB, Spurdle A, Beeghly-Fadiel A, Long J, Thompson D, Tomlinson I, Yu H, Lambrechts D, Dörk T, Goodman MT, Zheng Y, Salvesen HB, Bao PP, Amant F, Beckmann MW, Coenegrachts L, Coosemans A, Dubrowinskaja N, Dunning A,Runnebaum IB, Easton D, Ekici AB, Fasching PA, Halle MK, Hein A, Howarth K, Gorman M, Kaydarova D, Krakstad C, Lose F, Lu L,Lurie G, O'Mara T, Matsuno RK, Pharoah P, Risch H, Corssen M, Trovik J, Turmanov N, Wen W, Lu W, Cai Q, Zheng W, Shu XO. Polymorphisms in inflammation pathway genes and endometrial cancer risk. Cancer Epidemiol Biomarkers Prev 2013; 22: 216-223.

39) Lin MC, Burkholder KA, Viswanathan AN, Neuberg D, Mutter GL. Involution of latent endometrial precancers by hormonal and non hormonal mechanisms. Cancer 2009; 115: 2111-2118.

40) Mauland KK, Ju Z, Tangen IL, Berg A, Kalland KH, Øyan AM, Bjørge L, Westin SN, Krakstad C, Trovik J, Mills GB, Hoivik EA, Johanna Werner HM. Proteomic profiling of endometrioid endometrial cancer reveals differential expression of hormone receptors and MAPK signaling proteins in obese versus non-obese patients. Oncotarget 2017; 8: 106989-107001.

41) Wang ZM, Wan XH, Sang GY, Zhao JD, Zhu QY, Wang DM. miR-15a-5p suppresses endometrial cancer cell growth via Wnt/β-catenin signaling pathway by inhibiting WNT3A. Eur Rev Med Pharmacol Sci 2017; 21: 4810-4818.

42) Garmpis N, Damaskos C, Garmpi A, Spartalis E, Kalampokas E, Kalampokas T, Margonis GA, Schizas D, Andreatos N, Angelou A, Lavaris A, Athanasiou A, Apostolou KG, Spartalis M, Damaskou Z, Daskalopoulou A, Diamantis E, Tsivelekas K, Alavanos A, Valsami S, Moschos MM, Sampani A, Nonni A, Antoniou EA, Mantas D, Tsourouflis G, Markatos K, Kontzoglou K, Perrea D, Nikiteas N, Kostakis A, Dimitroulis D. Targeting histone deacetylases in endometrial cancer: a paradigm-shifting therapeutic strategy? Eur Rev Med Pharmacol Sci 2018; 22: 950-960.

43) Mehnert JM, Panda A, Zhong H, Hirshfield K, Damare S, Lane K, Sokol L, Stein MN, Rodriguez-Rodriquez L, Kaufman HL, Ali S,Ross JS, Pavlick DC, Bhanot G, White EP, DiPaola RS, Lovell A, Cheng J, Ganesan S. Immune activation and response to pembrolizumab in POLE -mutant endometrial cancer. J Clin Invest 2016; 126: 2334-2340.

44) Zhang HM, Fan TT, Li W, Li XX. Expressions and significances of TTF-1 and PTEN in early endometrial cancer. Eur Rev Med Pharmacol Sci 2017; 21: 20-26.