Krawczyk Dominika, Kwiatkowska Agnieszka. Novel promising biomarkers in endometrial cancer - review. Journal of Education, Health and Sport. 2019;9(8):783-794. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3407973
http://ojs.ukw.edu.pl/index.php/johs/article/view/7252

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 05.07.2019. Revised: 25.07.2019. Accepted: 17.08.2019.

Novel promising biomarkers in endometrial cancer- review

Dominika Krawczyk, Agnieszka Kwiatkowska

Abstract:

Introduction: Endometrial carcinoma is the most common gynaecological neoplasm in developed countries. The disease is mostly asymptomatic at an early stage, however there is no direct marker which could result in detection of cancer earlier. Nowadays the diagnosis is based on the histopathological results of endometrial biopsy.

Purpose: The aim of the review was to present the noticable studies that have showed the molecular markers and their usefulness in treatment options of endometrial cancer. We will review the current status of biomarkers which may be helpful in early diagnostic and further therapy of endometrial cancer.

State of knowledge: There have been many promising biomarkers which were described in newest studies. TFL is a tumor suppressor gene that contributes to cell-cycle arrest and RNA regulations. CD44 and JAK2 may be liked with neovascularity in distance tissue. Elevated levels of TGM2 and ASRGL1 are associated with an aggressive cancer phenotype and drug resistance in endometrial cancer. Additionally, the level of EpCAM were significantly increased in endometrial cancer sample comparing to control samples. AURKA results in resistance to anticancer agents including paclitaxel and docetaxel used in cancer treatment.

Summary: Endometrial cancer is a common problem among gynecological patients. There is no explicit marker which could directly contribute to biologic aggressiveness and response to treatments of that cancer. Presented molecules could potentially be a candidates biomarkers for diagnosis and further treatment of endometrial cancer. However, it is crucial to intensify

affords to better understand the impact of these markers. Which could lead to significant improvement of patient's survival and better quality of life.

Key words: Biomarkers; endometrial cancer; novel plasma markers;

Introduction and purpose

Endometrial carcinoma is the most common gynaecological neoplasm in developed countries, one in fourth causes of cancer in woman with increasing incidence [1,2]. In 2018, the International Agency for Research on Cancer recorded 382,069 of new cases of endometrial cancer (Crude rate: 10.1, World ASR: 8.4) and 89 929 women died because of this disease (Crude rate: 2.4, World ASR: 1,8) [3]. Endometrial cancer is found primarily in postmenopausal women, only in 5% of cases it occurs before the age of 40. Incidence peak falls on the sixth-seventh decade of life [4].

Risk factors of endometrial cancer include obesity and overweight (often as components of the metabolic syndrome), nulliparity, infertility (including polycystic ovary syndrome related infertility), diabetes, early onset of menstruation, late menopause, hormone replacement therapy, oestrogen-secreting tumours as well as treatment with tamoxifen in postmenopausal women [5,6,7].

About 30% of women with confirmed hyperplasia with atypia develop cancer. In women of reproductive age, factors such as primary ovulation disorders (ovulation), hormone-active tumours or side effects of applied hormonotherapy (eg stimulation of ovulation) contribute to the occurrence of abnormal hypertrophy of the uterus tissue[4].

There are two broad types of endometrial carcinoma, type I (endometrioid adenocarcinoma- 80-90% of all diagnoses) and type II (non-endometriotic adenocarcinoma including serous cancer, clear cell carcinoma, undifferentiated and mixed tumours such as malignant mixed Mullerian tumour- MMMT)[5]. The most important clinicopathological features of types I and II endometrial carcinoma are presented in Table 1

In women with Lynch syndrome (hereditary cancer large intestine not associated with polyposis – hereditary nonpolyposis colorectal cancer, HNPCC) endometrial cancer (mainly type I) is often inherited [5,8].

Improvement in diagnostics based on immunohistochemical markers and methods of retrieval antigens resulted in the creation of new classification of endometrial carcinomas by WHO in 2014. This classification is based on morphology and pathologists in their practice often use a variety of immunohistochemical markers to diagnose problematic neoplasms [10]. However, there are still classification difficulties, especially with "high quality endometrium cancer" (serous, clear cells, grade III endometriotic, mixed, undifferentiated and undifferentiated carcinomas and carcinosarcoma) [11,12,13].

In 2013, TCGA published a seminal comprehensive molecular study of 373 endometrial carcinomas. The study was restricted to endometrioid, serous and mixed endometrioid and serous carcinomas with no inclusion of other high-grade endometrial carcinomas, such as clear cell, undifferentiated and carcinosarcoma [14] The immunophenotype of different types of endometrial carcinoma are presented in Table 2.

The TCGA study revealed that endometrial carcinoma is a complex disease consisting of four intrinsic molecular subtypes: POLE (ultramutated), microsatellite instability (MSI) (hypermutated), copy number low (also referred to as microsatellite stable or no specific molecular profile) and copy number high (serous-like)[15,16]. The TCGA study showed that the four molecular subtypes are of prognostic significance [1].

Endometrial cancer Screening

Currently, there are no indications for prophylactic examinations for endometrial cancer in general population of women [5].

Women with obesity, polycystic ovary syndrome, diabetes or infertility should be monitored annually including gynaecological examination and transvaginal ultrasonography. Special care is given to carriers of mutations in mutator genes (syndrome Lynch), who are over 35 years old and who should have regular gynaecological control including the gynaecological examination, transvaginal ultrasound and endometrial aspiration biopsy. After the age of 40 they should be offered a surgery reducing the risk of developing ovarian and endometrial cancer [18,19]. The diagnosis is based on the histopathological results of endometrial biopsy during classic diagnostic curettage of the uterine cavity, a targeted biopsy during hysteroscopy or aspiration biopsy [5].

Description of the state of knowledge

Selected endometrial cancer biomarkers

Transformed follicular lymphoma (TFL)

Transformed follicular lymphoma (TFL) is identified as a gene on human chromosome 6q25.1, where the estrogen receptor alpha (ERa) and gene ESR1 are also located. ERa expression status is a validated prognostic molecular marker in early-stage endometrial cancer, but it is not unambiguour for the advanced stage of that cancer [20-23]. TFL is a potential tumor suppressor gene that contributes to cell-cycle arrest and RNA regulations [24].

Senn Wakahashi et al. conducted a study on 103 patients with endometrial cancer of III–IV FIGO stages. TFL expression in cancer tissue was significantly higher than in control endometrial ones [25]. Lack of ERa expression is a poor prognostic factor in early endometrial cancer. Among 41 ERa-low patients, 10-year progression-free survival was significantly lower in 15 TFL-low cases (univariate analysis, P 1⁄4 0.055; multivariate analysis, HR 1⁄4 4.70; 95% CI, 1.68–13.20; P 1⁄4 0.003). The study shows that the lack of TFL expression is a significant independent predictor of poor prognosis for a malignant neoplasm. Additionally, it is an independent prognostic factor for an advanced status of that disease, regardless of ERa status.

Furthermore, localization of TFL in cytoplasmic granules may also indicate that TFL regulates cancer cell proliferation, migration, invasion, metastasis and treatment resistance via posttranscriptional modulation [24,26].

CD44

CD44 is a transmembrane glycoprotein also referred to as P-glycoprotein 1. It is encoded by a single gene on chromosome locus 11p13 [27,28]. As a multifunctional receptor it can control biological functions involved in cancer cell dissemination and metastasis. CD44 can be sequentially cleaved by membrane type 1 matrix metalloprotease (MT1-MMP) and then presenilin-1/γ secretase induced by ligands (osteopontin or hyaluronic acid) binding (29). CD44 can translocate into the nucleus to activate transcription of genes which are important in metastasis and cell survival [30].

In study conducted by Torres et al., the analysis of data revealed that concentration of CD44 was significantly increased in endometrial cancer comparing to control group [31]. It was also found that concentrations of the two stem-cell markers, CD44 and TGM2 were significantly correlated in endometrial cancer samples. These results correspond to results of increased CD44 expression in EC tissues [32,33].

Elbasateeny et al. reported that CD44 along with CD133 might participate in early-stage endometrial cancer carcinogenesis and their overexpression might facilitate early diagnosis of endometrial cancers [31,33].
The formation of new blood vessels (angiogenesis) is required for tumor cell to disseminate and migrate to distant organs. CD44 expression has that impact on endothelial cells and this controls the formation of blood vessels [34,35,36]. Therefore, inhibition of CD44 results in impaired formation of vessel-like networks [36,37]. Nevertheless, metastasis formation is also linked to vascular CD44 expression [37].
Additionally, CD44- HA interaction could be a potential target for reducing bone metastases. CD44 signaling in prostate cancer cells has also been involved in osteoclast differentiation and tumor metastasis [38].

Trans- glutaminase 2 (TGM2)

Transglutaminases (TG) belong to a family of structurally and functionally related enzymes that catalyse Ca2+-dependent post- translational modifications of proteins by introducing protein– protein cross-links, amine incorporation, and site-specific deamidation [39,40]. Trans- glutaminase 2 is expressed in almost all cell compartments such as the cytoplasm, mitochondria, recycling endosomes, and nucleus. It is also present on the cell surface and gets secreted to the extracellular matrix via non-classical mechanisms [41].
Analysis of data revealed that concentrations of TGM2 were significantly increased in endometrial cancer comparing to control samples. It was also found that concentrations of the two stem-cell markers, CD44 and TGM2 were significantly correlated in endometrial cancer samples [31].
Other studies indicate that cancer cells express elevated levels of TGM2, and elevated TGM2 levels are associated with an aggressive cancer phenotype and drug resistance in most of tumors [42]. Moreover, TGM2 levels are especially enhanced in the cancer stem cells, and TGM2 is required for their survival, migration and invasion [43].
TGM2, acting as a protein crosslinking enzyme, can modify the structure and stability of extracellular matrix (ECM) in a way that it supports integrin-dependent ECM binding and migration of cancer cells [44].

Epithelial cell adhesion molecule (EpCAM)

The epithelial cell adhesion molecule is a glycoprotein that was originally identified as a marker for carcinoma, attributable to its high expression on rapidly proliferating tumors of epithelial origin. Normal epithelial express EpCAM at a variable but generally lower level than carcinoma cells. The expression of EpCAM is restricted to normal epithelial cells. Recent works emphasized that EpCAM is also responsible for processes such as signaling, cell migration, proliferation. Also, differentiation of EpCAM is typically overexpressed in a variety of epithelial cancers [45,46]. Latest studies discover that concentrations of EpCAM, were significantly increased in endometrial cancer sample comparing to control samples. It was also found that concentrations of the two stem-cell markers, CD44 and TGM2 were significantly correlated with EC samples [31].

JAG2

JAG2 is a notch transmembrane ligand. Notch signalling is a conserved signalling pathway linked to the development of several cancers due to its role in cell fate, regulation of proliferation and cell death [47]. Within cancer, Notch signalling mediates hypoxia, invasion and chemoresistance and JAG2 expression in primary tumors has been correlated with vascular development and angiogenesis [48,49]. In addition, elevated levels of JAG2 result in

significant chemoresistance and when JAG2 is knocked down in mice, tumor cells become sensitive to chemotherapeutics (doxorubicin) [50].
Additionally, JAG2 has been shown to be a promising target in several cancer cell lines, as specific antibody– drug conjugates have resulted in tumor reduction [51]. Notch signaling has been identified as an important pathway for carcinogenesis of the endometrium [52].

Aurora kinase A (AURKA)
AURKA is a cell-cycle regulated kinase that functions in spindle formation and chromosome segregation during the M phase of the cell cycle [53]. Aurora kinase is over- expressed in many human cancer cell-derived cell lines and cancer tissues and is connected to carcinogenesis [54]. AURKA has been shown to be a downstream target of MAPK1, which is a major force in cellular proliferation in several cancer cells [55]. Several reports have shown that upregulation of AURKA results in resistance to anticancer agents including paclitaxel and docetaxel [56-60]. In various cancers AURKA has been noted to be a novel therapeutic target for the gynecological malignancies that are particularly resistance to taxanes [61].
Kurai et al found significantly increased expression of AURKA in endometrial cancer compared to normal proliferative tissue [62]. The gene was strongly correlated with overall patient survival in recent study [53]. In a microarray analysis of endometrial cancer tissue, Moreno-Bueno et al showed that AURKA is highly expressed in Type II adenocarcinoma [63].
Recent study has found an association of overexpression of AURKA with clinicopathological factors in endometrial cancer. Immunohistochemistry showed overexpression of AURKA in endometrial cancer tissues compared with normal endometrium, indicating that upregulation of AURKA is a frequent abnormality in endometrial cancer. Patients with over- expression of AURKA also tended to have shorter Disease-Free Survival and a higher recurrence rate. These results suggest that elevated AURKA tumor expression may be an indicator of rapid cell division, rather than the cause of a malignant phenotype [64].

Asparaginase-like protein 1 (ASRGL1)
Asparaginase-like protein 1 (ASRGL1) is an enzyme classified as a N-terminal nucleophile (Ntn) hydrolase, exhibiting both L-asparaginase and β-aspartyl peptidase activity [65]. In endometrial carcinoma loss of the gene encoding ASRGL1 has previously been reported as part of a 29-gene signature associated with features of aggressive disease and poor recurrence-free survival [66,67]. Loss of ASRGL1 in primary endometrial carcinoma has also been suggested to be an independent biomarker for disease-specific survival in a subgroup of patients with endometrioid endometrial carcinoma [68].
In Fonnes et. al. study ASRGL1 mRNA level was related to survival and ASRGL1 protein expression. Low expression of ASRGL1 protein and ASRGL1 mRNA predicted poor disease specific survival. Low ASRGL1 expression was less frequent in patients with low grade endometrioid primary tumors compared to high grade endometrioid and non-endometrioid primary tumors, and ASRGL1 was lost in most metastatic lesions. In a prospective setting ASRGL1 validates as a strong prognostic biomarker in endometrial carcinoma. Loss of ASRGL1 is associated with aggressive disease and poor survival and have independent prognostic value in the entire endometrial carcinoma patient population [69].

Summary
Throughout the years, the expression of many promising molecules and genes have been investigated predominantly in endometrial cancer tissues for diagnostic and prognostic purposes. Prognostic molecular markers for endometrial cancer have been described in

several studies, but are not used for treatment decision-making, because most markers correlate with histologic type and are restricted only to early-stage disease.
In this study we report novel, potential biomarkers that could offer a good diagnostic accuracy in diagnosis of endometrial cancer, which being reported recently as plasma markers.
In view of incomplete indication of the impact of presented biomarkers on endometrial cancer patients survival, these biomarkers could be developed into a companion diagnostic tool in the identification and classification of endometrial cancer. Moreover, implementation of promoting trials would improve patient selection for adjuvant treatment including targeted therapies, which will improve outcomes for women with that disease.
Endometrial cancer is a major issue for the health-care system because of its increasing incidence in high-income countries. Therefore, it is essential to intensify affords to better understand what molecular alterations are driving the progression of endometrial cancer and how they contribute to biologic aggressiveness and response to treatments. With multicenter collaboration, progress and success with development of rationale biomarker-driven therapeutic implication to significantly improve overall patient survival.

Abbreviations:
World ASR – World Age-Standardised Rate
CTNNB1 -Catenin beta-1
PTEN - phosphatase and tensin homolog deleted on chromosome ten
PIK3CA - Phosphoinositide-3-kinase
ARID1A - AT-rich interactive domain-containing protein 1A
TP53 - tumor protein 53
PPP2R1A - protein phosphatase 2 scaffold subunit Aalpha
WHO- World Health Organization
TCGA - The Cancer Genome Atlas
MSI- Microsatellite Instability
ESR1- Estrogen Receptor 1 Gene
FIGO- Estrogen Receptor 1 Gene

Table 1. Clinicopathological features of types I and II endometrial carcinoma – modified with permission from Bokhman [9].

Morphological subtypes	**Endometrioid and mucinous carcinomas – type I**	**Serous carcinoma and carcinosarcoma- type II**
Age	Mainly perimenopausal and early postmenopausal	Often late postmenopausal period
Association with hyperoestrogenism	Present	Absent
Menstrual function	History of anovulatory bleeding	Normal
Reproductive function	Frequent infertility	Normal
Precursor lesion	Atypical hyperplasia	Serous endometrial intraepithelial carcinoma
Obesity	Present	Absent
Hyperlipidemia	Present	Absent
Diabetes mellitus	Present	Absent
Hypertension	Associated with obesity and/or diabetes mellitus	Absent or not associated with obesity and/or diabetes mellitus
Hormone receptor status	Mostly positive	Positive or negative
Prognosis	Mostly good	Poor
Molecular events mutations	CTNNB1, PTEN, KRAS, PIK3CA, ARID1A mutations; microsatellite instability	TP53, PIK3CA, PPP2R1A mutations

Table 2. Characteristic immunophenotype of different types of endometrial carcinoma [1,14,17].

	Endometrioid	**Serous**	**Clear cell**	**Carcinosarcoma**	**Undifferentiated**
Hormone receptors (oestrogen receptor, progesterone receptor)	Usually positive; may be negative in high grade	Positive or negative	Negative	Positive or negative in epithelial component depending on morphological subtype; negative in stromal component	Negative
p53	Usually wild type; may be mutation-type in high grade	Mutation type	Usually wild type; uncommonly mutation type	Mutation type	Wild type
p16	Patchy/mosaic	Block-type in most	Patchy/mosaic	Block-type in most	Patchy/mosaic
p16	Patchy/mosaic	Block-type in most	Patchy/mosaic	Block-type in most	Patchy/mosaic
Napsin A	Negative	Negative	Positive	Negative	Negative
MMR (Mixmatch repair) proteins	Lost in some	Retained	Lost in some	Retained	Lost in some

List of references:

1. Reclassifying endometrial carcinomas with a combined morphological and molecular approach Joseph Carlsona,b and W. Glenn McCluggagec
2. Bulletin du Cancer Volume 104, Issue 12, December 2017, Pages 1022-1031 Bulletin du Cancer Synthèse Cancer de l'endomètre de stade précoce : implication clinique des modèles prédictifsEndometrial cancer: Predictive models and clinical impact, SofianeBendifallah1MarcosBallester12EmileDaraï12
3. https://www.iarc.fr (12.07.2019)
4. http://onkologia.org.pl/rak-trzonu-macicy/ (12.07.2019)
5. Recommendations of the Polish Gynecological Oncology Society for the diagnosis and treatment of endometrial cancer. Jacek Jan Sznurkowski, Paweł Knapp, Lubomir Bodnar, Mariusz Bidziński, Robert Jach et all, Curr Gynecol Oncol 2017, 15 (1), p. 34–44
6. B. Trabert, N.Wentzensen, A.S. Felix, H.P. Yang,M.E. Sherman, L.A. Brinton,Metabolic syndrome and risk of endometrial cancer in the United States: a study in the SEER-medicare linked database, Cancer Epidemiol. Biomark. Prev. 24 (2015) 261–267.

7. L.A. Brinton, B. Trabert, G.L. Anderson, et al., Serum estrogens and estrogen metabolites and endometrial cancer risk among postmenopausal women, Cancer Epidemiol. Biomark. Prev. 25 (2016) 1081–1089.
8. Colombo N, Creutzberg C, Amant F et al.; ESMO-ESGOESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2016; 27: 16–41.
9. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983; 15:10–17.
10. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. Lyon: International Agency for Research on Cancer; 2014.
11. Reclassifying endometrial carcinomas with a combined morphological and molecular approach Joseph Carlsona,b and W. Glenn McCluggagec
12. Gilks CB, Oliva E, Soslow RA. Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. Am J Surg Pathol 2013; 37:874–881.
13. Thomas S, Hussein Y, Bandyopadhyay S, et al. Interobserver variability in the diagnosis of uterine high-grade endometrioid carcinoma. Arch Pathol Lab Med 2016; 140:836–843.
14. Cancer Genome Atlas Research Network. Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013; 497:67–73.
15. R. Murali, R.A. Soslow, B. Weigelt, Classification of endometrial carcinoma: more than two types, Lancet Oncol. 15 (2014) e268–e278.
16. C. Kandoth, N. Schultz, A.D. Cherniack, et al., Integrated genomic characterization of endometrial carcinoma, Nature 497 (2013) 67–73.
17. Lucas E, Chen H, Molberg K, et al. Mismatch repair protein expression in endometrioid intraepithelial neoplasia/atypical hyperplasia: should we screen for lynch syndrome in precancerous lesions? Int J Gynecol Pathol 2018; 1–10;
18. Stelloo E, Bosse T, Nout RA, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer: a TransPORTEC initiative. Mod Pathol 2015; 28:636–644.
19. Lucas E, Chen H, Molberg K, et al. Mismatch repair protein expression in endometrioid intraepithelial neoplasia/atypical hyperplasia: should we screen for lynch syndrome in precancerous lesions? Int J Gynecol Pathol, 2018; 1–10;
20. Creasman WT. Prognostic significance of hormone receptors in endome- trial cancer. Cancer 1993;71:1467–70.
21. Engelsen IB, Stefansson IM, Akslen LA, Salvesen HB. GATA3 expression in estrogen receptor alpha-negative endometrial carcinomas identifies aggres- sive tumors with high proliferation and poor patient survival. Am J Obstet Gynecol 2008;199:543.
22. Kauppila AJ, Isotalo HE, Kivinen ST, Vihko RK. Prediction of clinical outcome with estrogen and progestin receptor concentrations and their relationships to clinical and histopathological variables in endometrial cancer. Cancer Res 1986;46:5380–4.
23. Wik E, Raeder MB, Krakstad C, Trovik J, Birkeland E, Hoivik EA, et al. Lack of estrogen receptor-alpha is associated with epithelial-mesenchymal transition and PI3K alterations in endometrial carcinoma. Clin Cancer Res 2013;19:1094–105.
24. Minagawa K, Katayama Y, Nishikawa S, Yamamoto K, Sada A, Okamura A, et al. Inhibition of G1 to S phase progression by a novel zinc finger protein p58TFL at P-bodies. Mol Cancer Res 2009; 7:880–9.
25. Senn Wakahashi, Fumi Kawakami, Kanako Wakahashi, Kentaro Minagawa, Keitaro Matsuo, Yoshio Katayama, Hideto Yamada, Toshimitsu Matsui and Tamotsu Sudo

Transformed Follicular Lymphoma (TFL) Predicts Outcome in Advanced Endometrial Cancer Cancer Epidemiol Biomarkers Prev August 1 2018 (27) (8) 963-969; doi: 10.1158/1055-9965.EPI-17-0762
26. Minagawa K, Katayama Y, Matsui T. TFL, a hidden post-transcriptional modulator behind inflammation. Inflammation and cell signaling 2014;1: e244.
27. Underhill, C. (1992). CD44: the hyaluronan receptor. J. Cell. Sci. 103(Pt 2), 293–298.
28. Iczkowski, K. A. (2010). Cell adhesion molecule CD44: its functional roles in prostate cancer. Am. J. Transl. Res. 3, 1–7.
29. Senbanjo, L. T. & Chellaiah, M. A. CD44: A Multifunctional Cell Surface Adhesion Receptor Is a Regulator of Progression and Metastasis of Cancer Cells. *Front Cell Dev Biol* **5**, 18, https://doi.org/10.3389/fcell.2017.00018 (2017).
30. Thorne, R. F., Legg, J. W., and Isacke, C. M. (2004). The role of the CD44 transmembrane and cytoplasmic domains in co-ordinating adhesive and signalling events. J. Cell Sci. 117(Pt 3), 373–380. doi: 10.1242/jcs.00954
31. CD44, TGM2 and EpCAM as novel plasma markers in endometrial cancer diagnosis Anna Torres1,2,3,5*, Małgorzata Pac-Sosińska1, Krzysztof Wiktor4, Tomasz Paszkowski2, Ryszard Maciejewski1 and Kamil Torres1
32. Wojciechowski M, Krawczyk T, Śmigielski J, Malinowski A. CD44 expression in curettage and postoperative specimens of endometrial cancer. Arch Gynecol Obstet. 2015;291:383–90.
33. Elbasateeny SS, Salem AA, Abdelsalam WA, Salem RA. Immunohistochemical expression of cancer stem cell related markers CD44 and CD133 in endometrial cancer. Pathol Res Pract. 2016;212:10–6.
34. Liesveld, J. L., Frediani, K. E., Harbol, A. W., DiPersio, J. F., and Abboud, C. N. (1994). Characterization of the adherence of normal and leukemic CD34+ cells to endothelial monolayers. Leukemia 8, 2111–2117.
35. Trochon, V., Mabilat, C., Bertrand, P., Legrand, Y., Smadja-Joffe, F., Soria, C., et al. (1996). Evidence of involvement of CD44 in endothelial cell proliferation, migration and angiogenesis in vitro. Int. J. Cancer 66, 664–668. doi: 10.1002/(SICI)1097-0215(19960529)66:5<664::AID-IJC14>3.0.CO;2-4
36. Savani, R. C., Cao, G., Pooler, P. M., Zaman, A., Zhou, Z., and DeLisser, H. M. (2001). Differential involvement of the hyaluronan (HA) receptors CD44 and receptor for HA-mediated motility in endothelial cell function and angiogenesis. J. Biol. Chem. 276, 36770–36778. doi: 10.1074/jbc.M102273200
37. Cao, G., Savani, R. C., Fehrenbach, M., Lyons, C., Zhang, L., Coukos, G., et al. (2006). Involvement of endothelial CD44 during in vivo angiogenesis. Am. J. Pathol. 169, 325–336. doi: 10.2353/ajpath.2006.060206
38. Gupta, A., Cao, W., and Chellaiah, M. A. (2012). Integrin αvβ3 and CD44 pathways in metastatic prostate cancer cells support osteoclastogenesis via a Runx2/Smad 5/receptor activator of NF-κB ligand signaling axis. Mol. Cancer 11:66. doi: 10.1186/1476-4598-11-66
39. Greenberg CD, Birckbichler PJ, Rice RH. Transglutaminases: mul- tifunctional cross-linking enzymes that stabilize tissues. FASEB J. 1991; 5: 3071-7.
40. Lorand L, Graham RM. Transglutaminases: crosslinking enzymes with pleiotropic functions. Nat Rev Mol Cell Biol. 2003; 4: 140- 56.
41. Belkin AM Extracellular TG2: emerging functions and regulation. FEBS J. 2011;278:4704–16. Huang L, Xu AM, Liu W. Transglutaminase 2 in cancer. Am J Cancer Res. 2015; 5: 2756-76.
42. Huang L, Xu AM, Liu W. Transglutaminase 2 in cancer. Am J Cancer Res. 2015; 5: 2756-7

43. Eckert RL, Fisher ML, Grun D, Adhikary G, Xu W, Kerr C. Trans- glutaminase is a tumor cell and cancer stem cell survival factor. Mol Carcinog. 2015; 54: 947-58.
44. Colligham RJ, Griffin M. Transglutaminase 2 cross-linking of matrix proteins: biological significance and medical applications. Amino Acids. 2009; 36: 659-70.
45. Momburg F, Moldenhauer G, Hammerling GJ, Moller P: Immunohis- tochemical study of the expression of a Mr 34,000 human epithelium- specific surface glycoprotein in normal and malignant tissues. Can- cer Res 1987, 47:2883–2891
46. Wang MH, Sun R, Zhou XM, Zhang MY, Lu JB, Yang Y, Zeng LS, Yang XZ, Shi L, Xiao RW, Wang HY, Mai SJ (2018). Epithelial cell adhesion molecule overexpression regulates epithelial-mesenchymal transition, stemness and metastasis of nasopharyngeal carcinoma cells via the PTEN/AKT/mTOR pathway. Cell Death Dis 9(1): 2. doi: 10.1038/s41419-017-0013-8
47. Sasnauskiene A, Jonušienė V, Krikštaponienė A, Butkyte S, Dabkevičienė D, Kanopiene D, et al. NOTCH1, NOTCH3, NOTCH4, and JAG2 protein levels in human endometrial cancer. Medicina. 2014;50:14–8.
48. Zou J, Li P, Lu F, Liu N, Dai J, Ye J, et al. Notch1 is required for hypoxia- induced proliferation, invasion and chemoresistance of T-cell acute lymphoblastic leukemia cells. J Hematol Oncol. 2013;6:1–13.
49. PietrasA,vonStedingkK,LindgrenD,PåhlmanS,AxelsonH.JAG2 induction in hypoxic tumor cells alters Notch signaling and enhances endothelial cell tube formation. Mol Cancer Res. 2011;9:626–36.
50. Vaish V, Kim J, Shim M. Jagged-2 (JAG2) enhances tumorigenic- ity and chemoresistance of colorectal cancer cells. Oncotarget. 2017;8:53262–75.
51. Sagert J, West J, Wong C, Desnoyers L, Vasiljeva O, Richardson J, et al. Abstract 2665: transforming Notch ligands into tumor-antigen targets: a Probody-Drug Conjugate (PDC) targeting Jagged 1 and Jagged 2. Cancer Res. 2014;74:2665.
52. JonusieneV,SasnauskieneA,LachejN,KanopieneD,DabkevicieneD, Sasnauskiene S, et al. Down-regulated expression of Notch signaling molecules in human endometrial cancer. Med Oncol. 2013;30:438.
53. Townsend MH, Ence ZE, Felsted AM, Parker AC, Piccolo SR, Robison RA, et al. Potential new biomarkers for endometrial cancer. Cancer Cell Int. 2019; 19:19. Epub 2019/01/27.
54. Marumoto t, Zhang D and Saya H: aurora-a - a guardian of poles. nat rev cancer 5: 42-50, 2005.
55. Townsend MH, Felsted AM, Ence ZE, Piccolo SR, Robison RA, O'Neill KL. Elevated expression of hypoxanthine guanine phosphoribosyltransferase within malignant tissue. Cancer Clin Oncol. 2017;6:19.
56. Do TV, Xiao F, Bickel LE, et al: aurora kinase a mediates epithelial ovarian cancer cell migration and adhesion. oncogene 33: 539-549, 2014.
57. Anand S, Penrhyn-lowe S and Venkitaraman ar: aurora-a ampli cation overrides the mitotic spindle assembly checkpoint, inducing resistance to taxol. cancer cell 3: 51-62, 2003.
58. Lin y, richards fM, Krippendorff Bf, et al: Paclitaxel and cyc3, an aurora kinase a inhibitor, synergise in pancreatic cancer cells but not bone marrow precursor cells. Br J Cancer 107: 1692 1701, 2012.
59. Long M, yin g, liu l, et al: adenovirus-mediated aurora a shrna driven by stathmin promoter suppressed tumor growth and enhanced paclitaxel chemotherapy sensitivity in human breast carcinoma cells. Cancer Gene Ther 19: 271 281, 2012.

60. Tanaka e, Hashimoto y, ito t, et al: the suppression of aurora-a/StK15/BtaK expression enhances chemosensitivity to docetaxel in human esophageal squamous cell carcinoma. Clin Cancer Res 13: 1331 1340, 2007.
61. Umene K, Banno K, Kisu i, et al: aurora kinase inhibitors: potential molecular-targeted drugs for gynecologic malignant tumors. Biomed rep 1: 335-340, 2013.
62. Kurai M, Shiozawa t, Shih Hc, et al: expression of aurora kinases a and B in normal, hyperplastic, and malignant human endometrium: aurora B as a predictor for poor prognosis in endometrial carcinoma. Hum Pathol 36: 1281-1288, 2005.
63. Moreno-Bueno g, Sánchez-estévez c, cassia r, et al: Differential gene expression pro le in endometrioid and nonendometrioid endometrial carcinoma: StK15 is frequently overexpressed and ampli ed in nonendometrioid carcinomas. Cancer Res 63: 5697 5702, 2003.
64. Umene K, Yanokura M, Banno K, Irie H, Adachi M, Iida M, et al. Aurora kinase A has a significant role as a therapeutic target and clinical biomarker in endometrial cancer. *Int J Oncol.* (2015) 46:1498– 506. doi: 10.3892/ijo.2015.2842
65. J.R. Cantor, E.M. Stone, L. Chantranupong, G. Georgiou, The human asparaginase-like protein 1 hASRGL1 is an Ntn hydrolase with beta-aspartyl peptidase activity, Bio- chemistry 48 (2009) 11026–11031.
66. H.B. Salvesen, S.L. Carter, M. Mannelqvist, A. Dutt, G. Getz, I.M. Stefansson, et al., In- tegrated genomic profiling of endometrial carcinoma associates aggressive tumors with indicators of PI3 kinase activation, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 4834–4839.
67. E. Wik, J. Trovik, K. Kusonmano, E. Birkeland, M.B. Raeder, I. Pashtan, et al., Endome- trial carcinoma recurrence score (ECARS) validates to identify aggressive disease and associates with markers of epithelial-mesenchymal transition and PI3K alter- ations, Gynecol. Oncol. 134 (2014) 599–606.
68. P.H. Edqvist, J. Huvila, B. Forsstrom, L. Talve, O. Carpen, H.B. Salvesen, et al., Loss of ASRGL1 expression is an independent biomarker for disease-specific survival in endometrioid endometrial carcinoma, Gynecol. Oncol. 137 (2015) 529–537
69. Fonnes T, Berg HF, Bredholt T, Edqvist P-HD, Sortland K, Berg A, et al. Asparaginase-like protein 1 is an independent prognostic marker in primary endometrial cancer, and is frequently lost in metastatic lesions. Gynecol Oncol. 2018; 148: 197–203. https://doi.org/10.1016/j.ygyno.2017.10.025 PMID: 29096882