Erciyes Med J 2022; 44(5): 495–500 • DOI: 10.14744/etd.2022.45220

ORIGINAL ARTICLE – OPEN ACCESS

Determination of Drug Sensitivity Subgroups in Endometrial Cancer Based on Renin Angiotensin System

Seyhan Türk

ABSTRACT

Objective: The renin angiotensin system (RAS) is a prognostic molecular target for a large cancer group and plays an essential role in cancer biology. This critical system affects tumor growth and spread, both directly and indirectly, including endometrial cancer (EC). RAS activation has been strongly associated with the expression of angiogenesis, metastasis, and pro-angiogenic factors. The aim of this study was to identify EC subgroups according to variations in RAS genes and evaluate the prediction of chemotherapy resistance.

Materials and Methods: Hierarchical clustering, variance, t-test, fold change, false discovery rate calculation, and gene-set enrichment analyses were performed using microarray and drug sensitivity data obtained from the Genomics of Drug Sensitivity in Cancer Project database and the European Molecular Biology Laboratory-European Bioinformatics Institute ArrayExpress (accession no: E-MTAB-783).

Results: Subgroups of endometrial cancer cell lines were determined based on the RAS gene family. These subgroups were associated with 2 critical chemotherapeutic agents: vinblastine and epothilone B. Important gene sets were identified in the subgroups.

Conclusion: Pharmacological effects of RAS genes may differ in EC cells, depending on the pathological behavior of genomic subtypes. The results of this study showed that RAS genes were potential biomarkers for drug sensitivity and prognosis of endometrial cancer. RAS and NOTCH/autophagosome pathways may be related in EC. If the data of this study are confirmed by *in vitro* experiments and clinical samples, RAS genes would seem to be robust prognostic biomarkers for vinblastine and epothilone B.

Keywords: Endometrial cancer, epothilone B, gene biomarker, renin angiotensin system

Cite this article as:
Türk S. Determination of Drug Sensitivity Subgroups in Endometrial Cancer Based on Renin Angiotensin System. Erciyes Med J 2022; 44(5): 495-500.

Department of Biochemistry, Hacettepe University Faculty of Pharmacy, Ankara, Türkiye

Submitted
17.09.2021

Accepted
18.03.2022

Available Online
15.08.2022

Correspondence
Seyhan Türk,
Hacettepe University Faculty of Pharmacy, Department of Biochemistry, Ankara, Türkiye
Phone: +90 312 305 14 99
e-mail:
seyhan.turk@hacettepe.edu.tr

INTRODUCTION

Cancer treatment has evolved into a more personalized approach that takes into account specific conditions, such as unique genetic defects, in contrast to the traditional "one regimen for all patients" approach. Cancer chemotherapeutics are now widely used as cytotoxic agents targeting a specific type of cancer. Yet, despite progress, important unsolved challenges regarding prevention, early detection, and the development of innovative systemic medicines to improve therapeutic resistance still remain. Advances in genome and transcriptome sequencing and editing technologies continue to drive a shift to cancer precision treatment (1). Personalized medicine that can provide more effective therapy requires biomarker characterization to guide precise decision-making.

The renin angiotensin system (RAS) is made up of several gene products that regulate blood pressure, kidney vascular resistance, and the fluid and electrolyte balance (2, 3). The RAS has an important homeostatic role and may contribute to local tissue malfunction and illnesses (4). Local RAS management using various enzymes, peptides, and feedback mechanisms, may also be a therapy target for clinical neoplasia control (5–7). ATP6AP2, AGTR1, AGTR2, and ACE2 proteins, important members of the RAS family, are abundantly expressed in a cancerous endometrium (8). In some studies, it has been reported that the RAS gene family may be a biomarker for some cancer types and chemotherapeutic agents (9, 10).

Endometrial cancer (EC) is the world's most widespread gynecological malignancy (11, 12). Endometrial RAS irregularities can lead to EC vulnerability. Both glandular and stromal cells in the endometrium express RAS components (13). Through the prorene/ATP6AP2 and AngII/AGTR1 pathways, abnormal activation of endometrial RAS can lead to the development and progression of EC (8).

One of the most effective and successful means of cancer classification is greater definition of the roles of genes that function in the formation and biology of cancer as prognostic and chemotherapeutic markers. The aim of this study was to define EC subgroups based on the RAS gene family and to see if the resulting tumor subtypes differed in response to therapy.

MATERIALS and METHODS

Microarray Gene Expression Data

The gene expression data used in this study were obtained from the Genomics of Drug Sensitivity in Cancer Project (GDSC) database (http://www.cancerrxgene.org/) as well as the European Molecular Biology Laboratory-European Bioinformatics Institute ArrayExpress (accession number E-MTAB-783) (14). Robust multiarray average normalization of all of the values in the GDSC microarray dataset was performed using Affymetrix HT-HG-U133A v2 (Thermo Fisher Scientific, Waltham, MA, USA) and BRB-Array Tools software v4.6.1 (Biometric Research Program, National Institutes of Health, Bethesda, MD, USA) (15). The E-MTAB-783 database contained data for 13,513 genes, amounting to 22,279 probe sets. The data represented 773 cell lines of different cancer types. All gene transcript data for 7 EC cell lines (MFE296, ESS1, MFE280, AN3CA, HEC1, SNGM, and COLO68) and the IC50 values for 250 drugs of these cell lines were selected for in silico analysis of drug sensitivity (14).

Hierarchical Cluster Analysis

Hierarchical cluster analysis was performed to select subgroups of EC cell lines based on RAS gene transcripts. Cluster 3.0 (http://bonsai.hgc.jp/~mdehoon/software/cluster/software.htm) and Treeview 3.0 (http://jtreeview.sourceforge.net/) were used to conduct hierarchical cluster analysis using the Euclidean distance and complete linkage. The data were standardized after cluster analysis. Treeview 3.0 was used to view the standardized data. The subgroups were determined based on RAS gene transcript expression levels according to the hierarchical clustering. Five RAS family genes (ACE, CTSG, MAS1, CMA1, and RNPEP) were downregulated in Group A, while same genes were upregulated in Group B. Group A also comprised MFE296, ESS1, and MFE280, while Group B included the HEC1, SNGM, COLO684 cell lines.

Variance, T-test, Fold Change Analysis

After subgroups were determined based on the RAS gene findings, the mean IC50 value for each drug was determined using the drug IC50 information of the cell lines for each subgroup. The cell lines of each group must have a similar sensitivity profile for the same drug to achieve reliable results. Variance analysis was used to determine drugs with a variance value of <0.5 in each group, and the cut point was used to eliminate the appropriate drugs.

In order to compare the resistance profiles of the selected drugs, the IC50 data of each drug in the determined groups were compared using the fold change and t-testing. A t-test with a p value of <0.05 and a fold change of >3 were selected. Microsoft Excel 2010 software (Microsoft Corp., Redmond, WA, USA) was used to perform the variance, t-test, and fold change analysis.

False Discovery Rate Calculation

The Benjamini-Hochberg method was used to calculate the false discovery rate and modified p value using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA). The Benjamini-Hochberg approach for testing several independent hypotheses at the same time reduces the false discovery rate, which is defined as the ratio of false positive results to the number of total positive results.

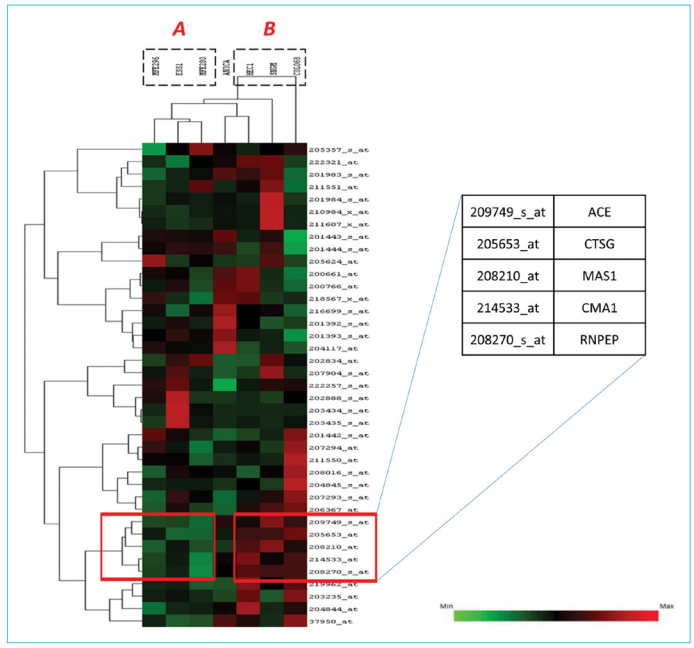

Figure 1. Two groups of renin angiotensin system genes with different expression values in endometrial cancer cell lines. Low expression was seen in Group A, while high expression was seen in Group B

Gene Set Enrichment Analysis

Gene Set Enrichment Analysis (GSEA) guidelines (http://software.broadinstitute.org/gsea/docGSEAUserGuideFrame.html) were used to perform the analyses. There are 22,279 probe set IDs in the dataset (E-MTAB-783), which were collapsed into 13,513 genes. The analysis was conducted using the Gene Ontology v6.1 database (http://geneontology.org/). Default filtering criteria were used, including gene sets with a size of 15–500. After applying the filter, 4081 gene sets were analyzed.

Probe set IDs are narrowed to gene symbols when a gene has more than 1 probe, the highest expression is selected, and the "maximum probe" is selected as the separation mode. GSEA analysis was performed to determine which genes significantly differed between the 2 groups.

RESULTS

The RAS gene family consists of 25 genes corresponding to 39 probes on the Affymetrix HG-U133 A&B microarray platforms (14). Cytotoxicity and gene expression data against 250 drugs were obtained from the database and normalized for 7 EC cell lines. Hierarchical cluster analysis was performed and it was determined that 5 genes (ACE, CTSG, MAS1, CMA1, RNPEP) in the RAS gene family divide EC cell lines into 2 groups (Fig. 1). The AN3CA cell line differed in group A (low gene expression) and group B (high gene expression). This appears to be an intermediate cell line, and was therefore excluded. Genes in Group A had a low expression value, while Genes in Group B had a higher expression value.

It is very important that the cells in each group have similar sensitivity to the same drug to compare the drug sensitivity pro-

Table 1. IC50 variance values of drugs with a variance values <0.5 by group

Drugs	Group A SD	Group B SD
FK866	0.0033	0.0035
QLVIII58	0.0082	0.1989
Thapsigargin	0.0199	0.0714
Bryostatin 1	0.0209	0.0118
Epothilone B	0.0266	0.0035
GSK2126458	0.0341	0.1133
LAQ824	0.0374	0.0073
Elesclomol	0.0472	0.0410
Vinorelbine	0.0472	0.0070
Docetaxel	0.0496	0.0149
Camptothecin	0.0507	0.0106
SN38	0.0817	0.0407
Ispinesib mesylate	0.1056	0.2866
Vinblastine	0.1373	0.0022
BEZ235	0.1618	0.0179
AUY922	0.2054	0.0245
Tivozanib	0.4954	0.2365

Table 2. Comparison of drugs with similar sensitivity profile within each group. Two drugs that were statistically significant (p<0.05 and fold change value >3) were selected

Drugs	p	Fold change
Vinblastine	0.044	12.474
Epothilone B	0.048	4.110
BEZ235	0.405	3.010
AUY922	0.465	4.314
Vinorelbine	0.496	3.319

files correctly and reliably. Therefore, the variance value was calculated for each drug in the groups. A total of 17 drugs with variance values of <0.5 were determined in both groups (Table 1). The IC50 values of 5 drugs with a fold change value >3 among the 17 drugs in Group A and Group B are shown in Figure 2. The p values and fold change values of these drugs are shown in Table 2.

Drug sensitivity comparison profiles in the 2 groups yielded 2 drugs, vinblastine, epothilone B, that had a p value of <0.05 and a fold change of >3 (Fig. 3).

GSEA of 2 groups of EC cell lines highlighted sequences of genes that differ significantly between the groups and provide insight into the pathways where these important gene sequences are located. When we compared the 2 groups in terms of enriched gene sequences, a positive correlation was found with Group A. A total of 3292 gene sets were enriched for Group A. Two pathways with a nominal p value <0.05, a q value (false discovery rate-adjusted p value) of <0.25, and apparent significant gene expressions were selected. Thus, autophagosome regulation genes and NOTCH receptor target genes pathways were determined (Fig. 4a, b). Table 3 shows most significant gene sets enriched in phenotype group A.

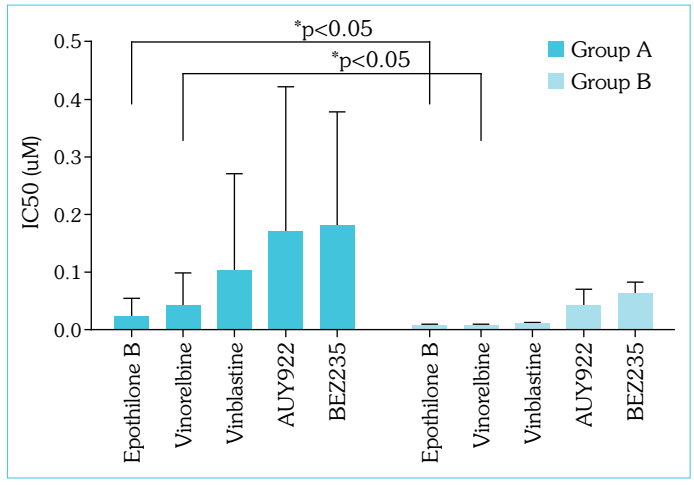

Figure 2. Comparison of 5 drugs with a fold change value >3 in the 2 groups. SD <0.5 in both groups

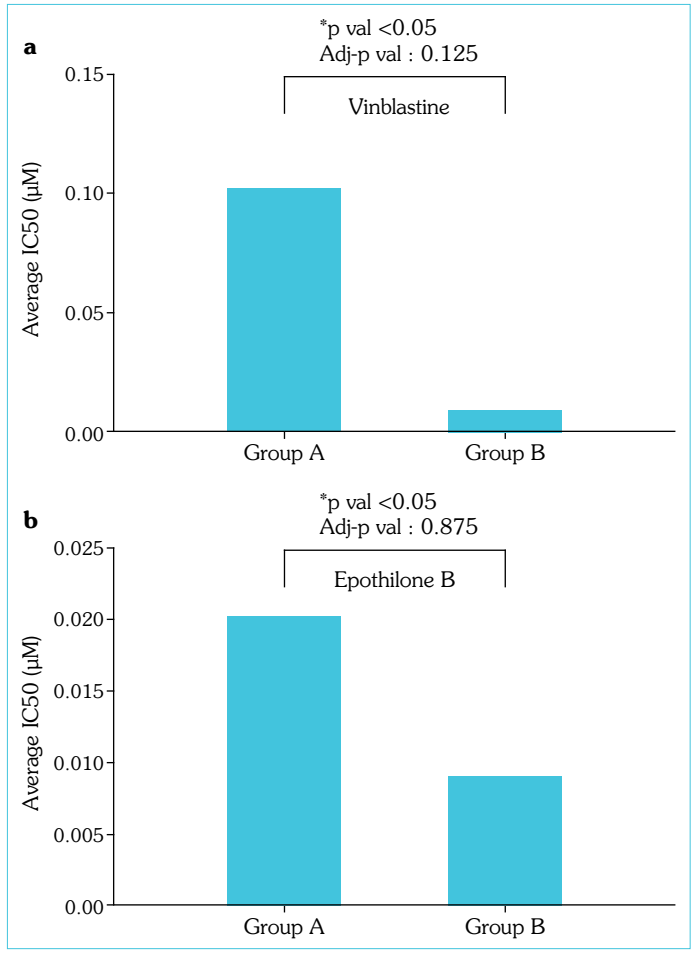

Figure 3. Average IC50 values in Group A and B cell lines of vinblastine and epothilone B, which had high fold values that were statistically significant in a group comparison

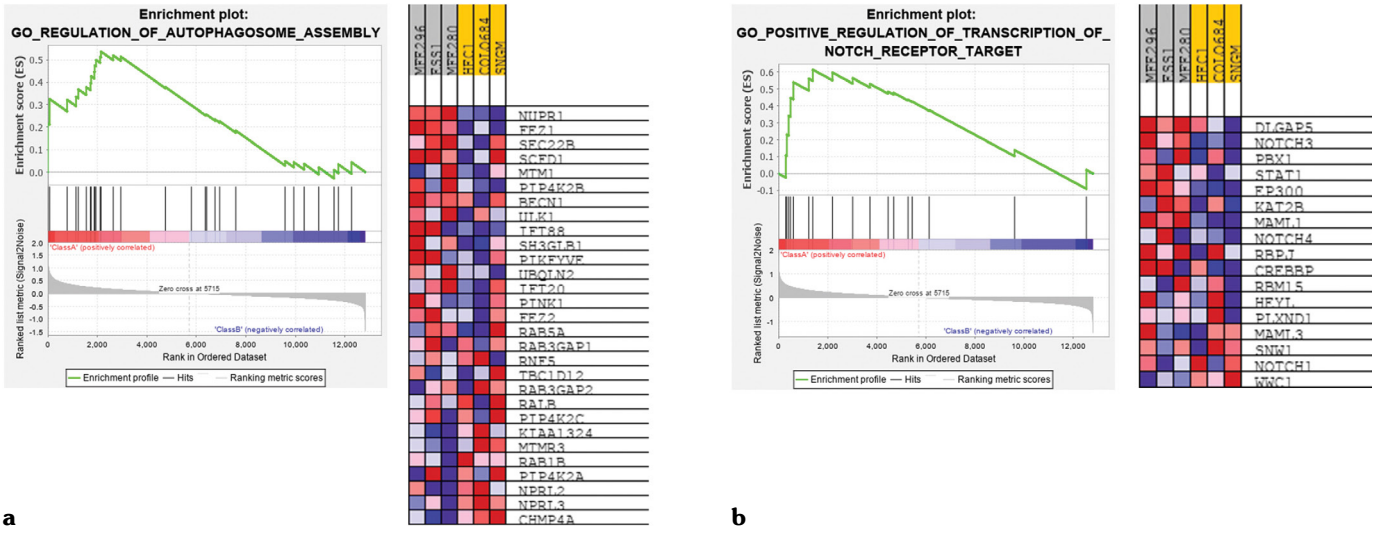

Figure 4. Gene set enrichment analysis. (a) NOTCH; (b) Autophagosome showing a positive correlation with Group A

Table 3. Gene sets enriched in phenotype Group A

Name	Size	Es	Nes	NOM p val
GO_POSITIVE_REGULATION_OF_TRANSCRIPTION_OF_NOTCH_R	25	0.5267	162.873	0
GO_REGULATION_OF_AUTOPHAGOSOME_ASSEMBLY	29	0.5370	159.598	0.01392
GO_SPINDLE_LOCALIZATION	45	0.5858	158.141	0.09623
GO_CORE_PROMOTER_SEQUENCE_SPECIFIC_DNA_BINDING	39	0.4549	158.138	0
GO_TRANSLATION_INITIATION_FACTOR_BINDING	29	0.4349	157.875	0
GO_PROSTATE_GLAND_MORPHOGENESIS	24	0.6824	155.327	0
GO_POSITIVE_REGULATION_OF_NEUROBLAST_PROLIFERATION	21	0.6187	155.234	0
GO_CILIARY_TIP	34	0.5854	15.516	0
GO_ADP_BINDING	38	0.4413	155.139	0
GO_SEX_CHROMOSOME	17	0.6127	153.753	0
GO_INTRACILIARY_TRANSPORT_INVOLVED_IN_CILIUM_AS	32	0.5483	152.921	0
GO_NEURAL_TUBE_PATTERNING	30	0.5894	152.537	0
GO_PROSTATE_GLAND_DEVELOPMENT	43	0.6037	152.081	0
GO_PROTEIN_K63_LINKED_DEUBIQUITINATION	26	0.5029	151.731	0
GO_DOSAGE_COMPENSATION	15	0.5717	151.528	0
GO_ESTABLISHMENT_OF_MITOTIC_SPINDLE_LOCALIZATION	33	0.5989	150.791	0.09563
GO_REGULATION_OF_HAIR_FOLLICLE_DEVELOPMENT	19	0.6653	150.479	0
GO_PROTEIN_LOCALIZATION_TO_CILIUM	39	0.4992	150.083	0
GO_REGULATION_OF_ANIMAL_ORGAN_FORMATION	31	0.5714	150.055	0
GO_MORPHOGENESIS_OF_AN_EPITHELIAL_FOLD	21	0.606	149.669	0.09563

DISCUSSION

The RAS has been noted in the development of EC and drug resistance pathways in numerous studies. For instance, the prorenin receptor, a component of the RAS, has been demonstrated to promote EC and glioblastoma via RAS signaling and to trigger the oncogenesis of pancreatic, colorectal, and brain malignancies via Wnt signaling (16). Our results show that EC cell lines can be subgrouped by genes in the RAS family (ACE, CTSG, MAS1, CMA1, RNPEP). It was determined that there was a significant difference between the 2 groups in the response to certain chemotherapeutic drugs. Two drugs, vinblastine and epothilone B, demonstrated a statistically significant difference in this study. Although the normal p value for vinblastine and epothilone drugs is statistically significant when comparing the 2 groups, the adjusted p value for both drugs was >0.05. The main reason for this may be the small number of samples in the groups, which is a limitation of this study. *In vitro* and clinical validation studies performed with large samples would be valuable.

The RAS of the female reproductive system is involved in a variety of physiological and pathological processes, such as follicular development, ovarian angiogenesis, and ovarian cancer progression. In 2020, Li et al. (17) revealed that during the mid-secretory phase, the key components of RAS, angiotensin II type-1 receptor (AT1R), and aldosterone synthase, are predominantly produced in the endometrial gland. In the stroma of the mid-secretory endometrium, the mineralocorticoid receptor, an aldosterone receptor, is enhanced.

Delforce et al. (8) analyzed levels of RAS gene expression and protein in 30 human formalin-fixed, paraffin-embedded endometrioid carcinomas and the adjacent endometrium. They identified differences in mRNA level between tumor and adjacent non-cancerous endometrium samples. All components of the RAS were expressed in most tumors and in the adjacent endometrium, and (pro) renin receptor/ATP6AP2, AGTR1, ACE1, and ACE2 mRNA levels were higher in the tumor tissue. Although the RAS family genes are expressed in EC, in our study, some genes demonstrated low expression in certain cancer cell lines, while others were high (Fig. 1).

A malfunctioning endometrial RAS could help cancer grow and spread. The overexpression of ATP6AP2, AGTR1, and ACE1, which are essential components of the RAS's proangiogenic pathway, suggests that the RAS is involved in EC growth and metastasis. As a result, anti-RAS drugs, which are now used to treat hypertension, could potentially be used to treat EC (8).

Piastowska-Ciesielska et al. (18) have identified an important association between AGTR1 and AGTR2 mRNA expression in Grade 1 and Grade 2 tumors. This suggests that AGTR1 and AGTR2 are linked, though the AGTR2 levels in low-grade cancers weren't particularly high. These and other findings indicate that the MAS1 gene could play a role in developing resistance to vinblastine and epothilone B drugs and contribute to the development of the tumor. Many studies have shown that the RAS has a crucial function in resistance to chemotherapy in different types of cancer (19–23). Another important finding of our study is that EC cell lines, which significantly express ACE, CTSG, MAS1, CMA1, and RNPEP genes, are approximately 12 and 4 times more sensitive to vinblastine and epothilone B drugs, respectively, compared with cells that have lower expression of these genes.

Clinical trials have been conducted to analyze the use of vinblastine in EC. Our results indicated that RAS genes have biomarker potential for vinorelbin and epothilone B. Considering the role of RAS in the development of cancer and chemotherapeutic resistance, it suggests that there may be an important relationship between the epothilone anticancer effect and RAS. The analyses conducted to determine the gensets of the EC subgroups based on RAS gene family revealed that the autophagosome and NOTCH gensets were positive in group A.

The NOTCH signal has a strong effect on the angiogenesis required for the development, progression, and metastasis of a tumor (24). The NOTCH signaling pathway is a highly preserved development pathway that significantly affects the coordination of cellular proliferation, distinction, and apoptosis. Deregulation of the NOTCH pathway has been associated with carcinogenesis in various cancers, including EC. Mismatch repair deficiency, as well as aberrant expression in key parts of the NOTCH and Hedgehog signaling pathways, could serve as independent prognostic indicators for recurrence and survival in patients with EC (25). The indications collectively suggest that advanced NOTCH1 levels aid tumor formation through several mechanisms. The underlying molecular pathways, however, have yet to be thoroughly elucidated.

It has previously been reported that the survival of the cell in the presence of nutrient deprivation and cellular suppression is affected by autophagy (26, 27). Autophagy has an important role in tumor formation and development, proliferation, drug resistance, immune regulation, and cell resistance to paclitaxel. The paclitaxel-induced autophagic response inhibits the death of EC cells (28). Treatment that inhibits autophagy -may be an efficient and powerful approach to the use of paclitaxel in EC treatment.

CONCLUSION

Our results indicating a positive correlation between the NOTCH and autophagosome pathways in Group A and a correlation with resistance are consistent with other findings in the literature. We concluded that RAS and the NOTCH/autophagosome pathways may be related in EC. If the data obtained in this study are confirmed by *in vitro* experiments and clinical samples, RAS genes would appear to be strong prognostic biomarkers for vinblastine and epothilone B.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author have no conflict of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

REFERENCES

1. Baltagiannis EG, Kyrochristos ID, Ziogas DE, Goussia A, Mitsis M, Roukos DH. From personalized to precision cancer medicine. Per Med 2020; 17(4): 245–50. [CrossRef]
2. Chiong JR, Aronow WS, Khan IA, Nair CK, Vijayaraghavan K, Dart RA, et al. Secondary hypertension: current diagnosis and treatment. Int J Cardiol 2008; 124(1): 6–21. [CrossRef]
3. Bader M. Tissue renin-angiotensin-aldosterone systems: Targets for pharmacological therapy. Annu Rev Pharmacol Toxicol 2010; 50: 439–65. [CrossRef]
4. Haznedaroğlu IC, Tuncer S, Gürsoy M. A local renin-angiotensin system in the bone marrow. Med Hypotheses 1996; 46(6): 507–10.
5. Abali H, Güllü IH, Engin H, Haznedaroğlu IC, Erman M, Tekuzman G. Old antihypertensives as novel antineoplastics: angiotensin-I-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists. Med Hypotheses 2002; 59(3): 344–8. [CrossRef]
6. Ager EI, Neo J, Christophi C. The renin-angiotensin system and malignancy. Carcinogenesis 2008; 29(9): 1675–84. [CrossRef]
7. George AJ, Thomas WG, Hannan RD. The renin-angiotensin system and cancer: old dog, new tricks. Nat Rev Cancer 2010; 10(11): 745–59.
8. Delforce SJ, Lumbers ER, Corbisier de Meaultsart C, Wang Y, Proietto A, et al. Expression of renin-angiotensin system (RAS) components in endometrial cancer. Endocr Connect 2017; 6(1): 9–19. [CrossRef]
9. Turk S, Turk C, Akbar MW, Kucukkaraduman B, Isbilen M, Demirkol Canli S, et al. Renin angiotensin system genes are biomarkers for personalized treatment of acute myeloid leukemia with Doxorubicin as well as etoposide. PLoS One 2020; 15(11): e0242497. [CrossRef]
10. Khoshghamat N, Jafari N, Toloue-Pouya V, Azami S, Mirnourbakhsh SH, Khazaei M, et al. The therapeutic potential of renin-angiotensin

system inhibitors in the treatment of pancreatic cancer. Life Sci 2021; 270: 119118. [CrossRef]
11. Lindemann K, Vatten LJ, Ellstrøm-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer 2008; 98(9): 1582–5. [CrossRef]
12. Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, et al. Endometrial cancer: A society of gynecologic oncology evidence-based review and recommendations, part II. Gynecol Oncol 2021; 160(3): 827–34. [CrossRef]
13. Li XF, Ahmed A. Compartmentalization and cyclic variation of immunoreactivity of renin and angiotensin converting enzyme in human endometrium throughout the menstrual cycle. Hum Reprod 1997; 12(12): 2804–9. [CrossRef]
14. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature 2012; 483(7391): 570–5. [CrossRef]
15. Simon RM. Design and analysis of DNA microarray investigations. 1st ed. London: Springer; 2011.
16. Wang J, Nishiyama A, Matsuyama M, Wang Z, Yuan Y. The (pro)renin receptor: a novel biomarker and potential therapeutic target for various cancers. Cell Commun Signal 2020; 18(1): 39. [CrossRef]
17. Li SY, Song Z, Yan YP, Li B, Song MJ, Liu YF, et al. Aldosterone from endometrial glands is benefit for human decidualization. Cell Death Dis 2020; 11(8): 679. [CrossRef]
18. Piastowska-Ciesielska AW, Płuciennik E, Wójcik-Krowiranda K, Bieńkiewicz A, Bednarek A, Ochędalski T. Analysis of the expression of angiotensin II type 1 receptor and VEGF in endometrial adenocarcinoma with different clinicopathological characteristics. Tumour Biol 2012; 33(3): 767–74. [CrossRef]
19. Ino K, Shibata K, Kajiyama H, Yamamoto E, Nagasaka T, Nawa A, et al. Angiotensin II type 1 receptor expression in ovarian cancer and its correlation with tumour angiogenesis and patient survival. Br J Cancer 2006; 94(4): 552–60. [CrossRef]
20. Kinoshita J, Fushida S, Harada S, Yagi Y, Fujita H, Kinami S, et al. Local angiotensin II-generation in human gastric cancer: correlation with tumor progression through the activation of ERK1/2, NF-kappaB and survivin. Int J Oncol 2009; 34(6): 1573–82. [CrossRef]
21. Röcken C, Lendeckel U, Dierkes J, Westphal S, Carl-McGrath S, Peters B, et al. The number of lymph node metastases in gastric cancer correlates with the angiotensin I-converting enzyme gene insertion/deletion polymorphism. Clin Cancer Res 2005; 11(7): 2526–30.
22. Uemura H, Hasumi H, Ishiguro H, Teranishi J, Miyoshi Y, Kubota Y. Renin-angiotensin system is an important factor in hormone refractory prostate cancer. Prostate 2006; 66(8): 822–30. [CrossRef]
23. Rhodes DR, Ateeq B, Cao Q, Tomlins SA, Mehra R, Laxman B, et al. AGTR1 overexpression defines a subset of breast cancer and confers sensitivity to losartan, an AGTR1 antagonist. Proc Natl Acad Sci U S A 2009; 106(25): 10284–9. [CrossRef]
24. Rodriguez-Vita J, Tetzlaff F, Fischer A. Notch controls endothelial cells. Oncoscience 2017; 4(5-6): 45–6. [CrossRef]
25. Polychronidou G, Kotoula V, Manousou K, Kostopoulos I, Karayannopoulou G, Vrettou E, et al. Mismatch repair deficiency and aberrations in the Notch and Hedgehog pathways are of prognostic value in patients with endometrial cancer. PLoS One 2018; 13(12): e0208221.
26. Das G, Shravage BV, Baehrecke EH. Regulation and function of autophagy during cell survival and cell death. Cold Spring Harb Perspect Biol 2012; 4(6): a008813. [CrossRef]
27. Deng L, Feng J, Broaddus RR. The novel estrogen-induced gene EIG121 regulates autophagy and promotes cell survival under stress. Cell Death Dis 2010; 1(4): e32. [CrossRef]
28. Liu S, Li X. Autophagy inhibition enhances sensitivity of endometrial carcinoma cells to paclitaxel. Int J Oncol 2015; 46(6): 2399–408.