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Title: Determination of Depression, Anxiety, Stress and Emotional Reactions Experienced During the Covid-19 Pandemic Among Pregnant Cases

Running Title: RAS Genes as chemotherapy biomarkers in EC

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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. It, directly and indirectly, affects tumor growth and spread, including endometrial cancer. RAS activation has been strongly related to the expression of angiogenesis, metastasis, and pro-angiogenic factors. This study, aimed to identify the endometrial cancer subgroups according to the variations of Renin angiotensin system genes and to predict chemotherapy resistance.

METHODS: Hierarchical clustering, variance, t-test, fold change, false discovery rate calculation and gene set enrichment analyzes were performed using microarray and drug sensitivity data obtained from the Cancer Genome Project database (E-MTAB-783).

RESULTS: Subgroups of endometrial cancer cell lines were determined based on the Renin angiotensin system gene family. These subgroups were associated with two critical chemotherapeutic agents, Vinblastine and Epothilone B. Important gene sets among subgroups were identified.

CONCLUSION: Pharmacological effects of RAS genes may differ in endometrial cancer cells depending on the pathological behavior of genomic subtypes. Our results show that the genes in the Renin angiotensin system are potential biomarkers for drug susceptibility and prognosis of endometrial cancer. Renin angiotensin system and NOTCH / autophagosome pathways may be related to each other in endometrial cancer. In conclusion, if the data obtained in this study are confirmed by in vitro experiments and clinical samples, Renin angiotensin system genes are robust prognostic biomarkers for Vinblastine and Epothilone B.

Keywords: Renin Angiotensin System; Endometrial Cancer; Vinorelbine; Epothilone B; Gene Biomarker

INTRODUCTION

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Cancer chemotherapeutics as cytotoxic agents are widely used against a specific type of cancer. Cancer treatment has begun to evolve into a more personalized approach where it will be treated specially, taking into account the genetic defects of each patient, by changing the traditional “one regimen for all patients” approach. Despite prevention and treatment, important unsolved challenges include timely detection and the development of innovative systemic medicines to improve therapeutic resistance. Advancing genome and transcriptome sequencing and editing technologies are laying the groundwork for solving these unsolved issues, emphasizing the need to move from personalized to cancer precision treatment (1). Thus, personalized medicine for more effective therapy needs the characterization of biomarkers that will guide selected patients in decision-making.

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

Endometrial cancer (EC), 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 ways for cancer classification is defining 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 RAS gene family and see if the resulting tumor subtypes differed in their therapy responses.

METHODS and MATERIALS

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Microarray gene expression, obtaining and normalizing drug cytotoxicity data

The gene expression data used in this study obtained from the Cancer Genome Project (CGP) database (http://www.cancerrxgene.org/) as well as the accession number is E-MTAB-783 that was constructed by McDermott et al. (14). All values in the CGP microarray dataset were normalized by the RMA method using Affymetrix HT- HG-U133A v2 in the BRB-Array Tools software v4.6.1 (15). This database contains 13,513 gene data versus 22,279 probes. These data belong to 773 cell lines of different cancer types. All gene transcript data for seven endometrium cancer cell lines (MFE296, ESS1, MFE280, AN3CA, HEC1, SNGM, and COLO68) and IC50 values for 250 drugs of these cell lines were selected for drug susceptibility analysis in order to use in silico analysis (14).

Hierarchical cluster analysis

Hierarchical cluster analysis was made to decide the subgroups of EC cell lines based on RAS gene transcripts. Cluster 3.0 and Treeview 3.0 were used for hierarchical cluster analysis. In the hierarchical clustering using gene expression values, "Euclidean distance" and "Complete Linkage" were used as clustering methods. The data was standardized after cluster analysis (http://bonsai.hgc.jp/~mdehoon/software/cluster/software.htm). Treeview 3.0 was used to view the standardized data (http://jtreeview.sourceforge.net/). The subgroups were determined based on RAS gene transcripts expression levels according to the hierarchical clustering. Five RAS family genes (ACE, CTSG, MAS1, CMA1 and RNPEP) are downregulated in Group 1 (Group A), while same genes are upregulated in Group 2 (Group B). In addition, Group A consists of MFE296, ESS1, MFE280, while Group B includes HEC1, SNGM, COLO684 cell lines.

Variance, T-test, Fold change analysis

After subgroups were determined based on RAS genes, the mean IC50 values for each drug were determined using the drug IC50 information of the cell lines of each subgroup. The cell lines in each group must have a similar sensitivity profile for the same drug to achieve reliable results. With variance analysis, drugs with variance values less than 0.5 in each group were selected, and the drugs remaining on the cut point were eliminated.
In order to compare the resistance profiles of the selected drugs, IC50 data of each drug of the determined groups were compared with fold change and t-test. The t-test with a P value of less than 0.05 and a fold change of more than three were selected. Excel 2010 was used to do the variance, t-test, and fold change analysis.

**False discovery rate calculation**

Using Excel 2016, the Benjamini-Hochberg method was used to calculate the false discovery rate and modified p-value. The Benjamini and Hochberg approach for testing many independent hypotheses at the same time tries to reduce the false discovery rate, which is defined as the predicted ratio of false rejections to total rejections.

**Gene set enrichment analysis (GSEA)**

GSEA guideline were used for Gene set enrichment analyzes (http://software.broadinstitute.org/gsea/docGSEAUserGuideFrame.html). There are 22277 probeset IDs in the dataset (E-MTAB-783), which were collapsed into 13321 genes. The analysis was conducted using the "C5 all Gene ontology v6.1 database." We used default filtering criteria, including genesets with sizes between 15-500. After applying the filter, 4081 gene sets were analyzed.

Probeset IDs are narrowed to gene symbols where a gene has more than one probe, the highest expression is selected, and the "maximum probe" is selected as the separation mode. GSEA analysis was performed to determine which genes were significantly differ between two groups.

**RESULTS**

In the Cancer Genome Project (CGP) data, the RAS gene family comprises of 25 genes that correspond to 39 probes on Affymetrix HG-U133 A&B microarray platforms. The RAS gene family consists of 25 genes corresponding to 39 probes on Affymetrix HG-U133 A&B microarray platforms in the Cancer Genome Project (CGP) data (14). For 7 EC cell lines, cytotoxicity and gene expression data against 250 drugs were obtained from the CGP database and normalized. Hierarchical cluster analysis was performed with 25 gene expressions corresponding to 39 probes. As a result, it was determined that five genes (ACE, CTSG, MAS1, CMA1, RNPEP) in the RAS gene family divide Endometrial cancer cell lines into two groups.
(Figure 1). As seen from Figure 1, the AN3CA cell line differs from group A (those expressing these genes low) and group B (those expressing these genes high) when the expression of the specified genes is evaluated. This cell line appears to be intermediate. For this reason, it was excluded from the groups. Genes in Group 1 (Group A) have a low expression value, while Genes in Group 2 (Group B) have a higher expression value.

It is very important that the cells in each group have similar sensitivity to the same drug to compare the determined groups’ drug sensitivity profiles correctly and reliably. Therefore, the variance value was calculated for each drug in the groups. A total of 17 drugs with variance values below 0.5 were determined in both groups (Table 1). In Figure 2, IC50 values of 5 drugs with a fold change value over three between 17 drugs are shown for Group A and Group B (Figure 2). The p values and fold change values of these drugs are shown in table 2 (Table 2).

By comparing drug sensitivity profiles in two groups, two drugs vinblastine, epothilone B, which were below 0.05 and with a fold change above 3, were determined (Figure 3).

Gene-set enrichment analysis was done between A and B groups of EC cell lines. The analysis was done with all the genes in the E-MTAB-783 CGP database (14). The results highlight sequences of genes that differ significantly between the two groups and give insight into which pathways these important gene sequences are located in. When we compared the two groups in terms of enriched gene sequences, a positive correlation was found with group A. A total of 3292 genesets were enriched for group A. Two pathways with a nom P-value of less than 0.05, an FDR q value of less than 0.25, and apparent significant gene expressions were chosen. Thus, autophagosome regulation genes and NOTCH receptor target genes pathways were determined (Figure 4A and 4B). Table 3 shows most significant gene sets enriched in phenotype group A (Table 3).

**DISCUSSION**

RAS has been implicated in the development of endometrial cancer and drug resistance pathways in numerous studies. For instance, the prorenin receptor (PRR), a component of RAS, has been demonstrated to promote endometrial cancer and glioblastoma via RAS signaling and to trigger the oncogenesis of pancreatic, colorectal, and brain malignancies by Wnt signaling (16). Our results show that Endometrial cancer cell lines can be subgrouped with genes
belonging to the RAS family (ACE, CTSG, MAS1, CMA1, RNPEP). It was determined that there is a significant difference between these two groups against certain chemotherapeutic drugs. Two drugs that show statistically significant high differences, vinblastine and epothilone B, were determined in this study. Although the normal p-value for Vinblastine and Epothilone drugs is statistically significant when comparing the two groups, the adjusted p-value for both drugs is higher than 0.05. The main reason for this may be the low number of samples in the groups which is appear as the limit of this study. Suggesting in vitro and clinical validation studies should be performed with more samples.

The female reproductive system's RAS is engaged in a variety of physiological and pathological processes, such as follicular development, ovarian angiogenesis, and ovarian cancer progression. In 2020, Li et al. revealed that during the mid-secretory phase, the key components of RAAS, 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 (MR), an aldosterone receptor, is enhanced (17).

Delforce et al. analyzed levels of RAS gene expression and protein in thirty human endometrial carcinoma cells and their paraffin-embedded (FFPE) endometrium. They identified differences in mRNA abundance between tumor and matched adjacent non-cancerous endometrium (8). It has been observed that all apparatuses of RAS are expressed in tumor and endometrium; (pro) renin receptor / ATP6AP2, AGTR1, ACE1, and ACE2 mRNA levels were higher than non-cancerous endometrium. Although the RAS family genes are expressed in Endometrium cancer, in our study, as shown in Figure 1, some genes were expressed as low in certain cancer cell lines, and high in others.

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 way, suggests that the RAS is involved in endometrial cancer growth and metastasis. As a result, anti-RAS drugs, which are now used to treat hypertension, could potentially be used to treat endometrial cancer (8).

Piastowska-Ciesielska et al. have identified an important association between AGTR1 and AGTR2 mRNA expression in 1st and 2nd degree tumors (18). Suggests that AGTR1 and

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AGTR2 are linked, albeit AGTR2 levels in low-grade cancers aren't particularly high. By these data and besides this, it was concluded that the MAS1 gene could play a role in developing of resistance against vinblastine and epothilone B drugs and contribute to the development of the tumor. Many studies show that RAS has a crucial function in resistance to chemotherapy in different types of cancer (19-23). Another important finding in our study is that Endometrial cancer cell lines, which express ACE, CTSG, MAS1, CMA1, and RNPEP genes higher, are approximately 12 and 4 times more sensitive to vinblastine and epothilone B drugs compared to cells that express these genes lower.

There are clinical phase studies for the use of vinblastine in endometrial cancer. Our results show that RAS genes have biomarker potential for Vinorelbin and Epothilone B. Considering the roles of RAS in the development of cancer and chemotherapeutetic resistance, it suggests that there may be a serious relationship between the epothilone anticancer effect and RAS. As a result of the analyzes conducted to determine the gensets of the EC subgroups based on RAS gene family, the autophagosome and NOTCH gensets were found to be 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. MMRd, as well as aberrant expression of the key parts of the Notch and Hedgehog signaling pathways, could serve as independent prognostic indicators for recurrence and survival in patients with endometrial cancer, according to Genovefa et al. in 2018 (25). Whole indications show that advanced NOTCH1 levels aid tumor formation by several mechanisms. The underlying molecular pathways, however, have yet to be thoroughly elucidated.

It has been reported that the survival of the cell in the presence of nutrient deprivation and cellular suppression is affected by autophagy (26, 27). It has been stated that autophagy has important roles in tumor formation and development, proliferation, drug resistance, immune regulation and, plays roles in cell resistance to paclitaxel. The paclitaxel induced autophagic...
response has an impact on preventing the ultimate decease of the endometrial carcinoma (28). Autophagy inhibitor treatment can be an efficient and powerful approach to advance paclitaxel consequences in endometrial carcinoma treatment.

**CONCLUSION**

In the results we obtained, the positive correlation of NOTCH and autophagosome pathways in group A and their correlation with resistance are consistent with the information in the literature. It is concluded in this study that RAS and NOTCH / autophagosome pathways may be related to each other in endometrial cancer. In conclusion, if the data obtained in this study are confirmed by in vitro experiments and clinical samples, RAS genes are strong prognostic biomarkers for vinblastine and epothilone B.

**ACKNOWLEDGEMENT**

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**REFERENCES**


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Table 1. Group A and Group B IC50 variance values. List of drugs with variance values below 0.5.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Group A St Dev</th>
<th>Group B St Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>FK866</td>
<td>0.0033</td>
<td>0.0035</td>
</tr>
<tr>
<td>QLVIII58</td>
<td>0.0082</td>
<td>0.1989</td>
</tr>
<tr>
<td>Thapsigargin</td>
<td>0.0199</td>
<td>0.0714</td>
</tr>
<tr>
<td>Bryostatin 1</td>
<td>0.0209</td>
<td>0.0118</td>
</tr>
<tr>
<td>Epothilone B</td>
<td>0.0266</td>
<td>0.0035</td>
</tr>
<tr>
<td>GSK2126458</td>
<td>0.0341</td>
<td>0.1133</td>
</tr>
<tr>
<td>LAQ824</td>
<td>0.0374</td>
<td>0.0073</td>
</tr>
<tr>
<td>Elesclomol</td>
<td>0.0472</td>
<td>0.0410</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>0.0472</td>
<td>0.0070</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>0.0496</td>
<td>0.0149</td>
</tr>
<tr>
<td>Camptothecin</td>
<td>0.0507</td>
<td>0.0106</td>
</tr>
<tr>
<td>SN38</td>
<td>0.0817</td>
<td>0.0407</td>
</tr>
<tr>
<td>Ispinesib Mesylate</td>
<td>0.1056</td>
<td>0.2866</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>0.1373</td>
<td>0.0022</td>
</tr>
<tr>
<td>BEZ235</td>
<td>0.1618</td>
<td>0.0179</td>
</tr>
<tr>
<td>AUY922</td>
<td>0.2054</td>
<td>0.0245</td>
</tr>
<tr>
<td>Tivozanib</td>
<td>0.4954</td>
<td>0.2365</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>p value</th>
<th>Fold change</th>
</tr>
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<tbody>
<tr>
<td>Vinblastine</td>
<td>0.044</td>
<td>12.474</td>
</tr>
<tr>
<td>Epothilone B</td>
<td>0.048</td>
<td>4.110</td>
</tr>
<tr>
<td>BEZ235</td>
<td>0.405</td>
<td>3.010</td>
</tr>
<tr>
<td>AUY922</td>
<td>0.465</td>
<td>4.314</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>0.496</td>
<td>3.319</td>
</tr>
</tbody>
</table>

Table 3. Gene sets enriched in phenotype Group A

<table>
<thead>
<tr>
<th>NAME</th>
<th>SIZ E</th>
<th>ES</th>
<th>NES</th>
<th>NOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO_POSITIVE_REGULATION_OF_TRANSCRIPTION_OF_NOTCH_R</td>
<td>25</td>
<td>0.52</td>
<td>162.8</td>
<td>0</td>
</tr>
<tr>
<td>GO_REGULATION_OF_AUTOPHAGOSOME.Assembly</td>
<td>29</td>
<td>0.53</td>
<td>159.5</td>
<td>0.013</td>
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<tr>
<td>GO_SPINDLE_LOCALIZATION</td>
<td>45</td>
<td>0.58</td>
<td>158.1</td>
<td>0.096</td>
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<tr>
<td>GO_CORE_PROMOTER_SEQUENCE_SPECIFIC_DNA_BINDING</td>
<td>39</td>
<td>0.45</td>
<td>158.1</td>
<td>0</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>GO_TERM</th>
<th>COUNT</th>
<th>q-value</th>
<th>p-value</th>
<th>GO-DR</th>
<th>GO-DR (log2 fold change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO_TRANSLATION_INITIATION_FACTOR_BINDING</td>
<td>29</td>
<td>0.43</td>
<td>157.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GO_PROSTATE_GLAND_MORPHOGENESIS</td>
<td>24</td>
<td>0.68</td>
<td>155.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GO_POSITIVE_REGULATION_OF_NEUROBLAST_PROLIFERATION</td>
<td>21</td>
<td>0.61</td>
<td>155.2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>GO_CILIARY_TIP</td>
<td>34</td>
<td>0.58</td>
<td>15.51</td>
<td>0</td>
<td>0</td>
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<tr>
<td>GO_ADP_BINDING</td>
<td>38</td>
<td>0.44</td>
<td>155.1</td>
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<tr>
<td>GO_SEX_CHROMOSOME</td>
<td>17</td>
<td>0.61</td>
<td>153.7</td>
<td>0</td>
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<tr>
<td>GO_INTRACILIARY_TRANSPORT_INVOLVED_IN_CILIUM_AS</td>
<td>32</td>
<td>0.54</td>
<td>152.9</td>
<td>0</td>
<td>0</td>
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<tr>
<td>GO_NEURAL_TUBE_PATTERNING</td>
<td>30</td>
<td>0.58</td>
<td>152.5</td>
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<tr>
<td>GO_PROSTATE_GLAND_DEVELOPMENT</td>
<td>43</td>
<td>0.60</td>
<td>152.0</td>
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<tr>
<td>GO_PROTEIN_K63_LINKED_DEUBIQUITINATION</td>
<td>26</td>
<td>0.50</td>
<td>151.7</td>
<td>0</td>
<td>0</td>
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<tr>
<td>GO_DOSAGE_COMPENSATION</td>
<td>15</td>
<td>0.57</td>
<td>151.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GO_ESTABLISHMENT_OF_MITOTIC_SPINDLE_LOCALIZATION</td>
<td>33</td>
<td>0.59</td>
<td>150.7</td>
<td>0.095</td>
<td>63</td>
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<tr>
<td>GO_REGULATION_OF_HAIR_FOLLICLE_DEVELOPMENT</td>
<td>19</td>
<td>0.66</td>
<td>150.4</td>
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<td>0</td>
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<tr>
<td>GO_PROTEIN_LOCALIZATION_TO_CILIUM</td>
<td>39</td>
<td>0.49</td>
<td>150.0</td>
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</tbody>
</table>

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FIGURES
Figure 1. Two groups of RAS genes with different expression values in endometrial cancer cell lines. These genes are expressed low in group A, while high in group B.
Figure 2. 5 drugs with a floor change value above three between the groups. SD is below 0.5 in both groups.
Figure 3. Average IC50 values in group A and B cell lines of 2 drugs with high fold values and statistically significant as a result of group comparison. a. Vinblastine b. Epothilone B.
Figure 4. Gene set enrichment analysis. a. NOTCH, b. Autophagosome shows a positive correlation with group A.
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