CPED1 is differentially expressed in ovarian cancer.

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Ovarian cancer is most common reason for a gynecological cancer death in the developed world (1). There are zero targeted chemotherapies available for the treatment of ovarian cancer. We studied the transcriptomes of tumors from ovarian cancer by comparing them to the transcriptome of normal ovarian tissue using two separate datasets (2, 3). We found that the cadherin-like and PC esterase domain containing 1, CPED1, was among the genes whose expression changed the most between ovarian tumors and the normal ovary. This is the first report of differential expression of CPED1 in ovarian cancer.

Keyword: ovarian cancer, differential gene expression, systems oncology, CPED1, tumor transcriptome analysis, targeted therapeutics in ovarian cancer.

Introduction

Ovarian cancer was diagnosed in 24,000 women in the United States in 2018 and in the same year 17,000 women expired from the disease (4). Ovarian cancer is the fifth leading cause of cancer death for women in the United States (1). Standard chemotherapy includes the use of a platinum-taxane combination and bevacizumab can be added to this (5). There are zero targeted treatment options available for women diagnosed with ovarian cancer.

Here, we studied the transcriptomes of ovarian tumors isolated from women diagnosed with ovarian cancer to understand in an unbiased fashion how gene expression was most different between ovarian tumors and the normal ovary, by comparing the transcriptomes of ovarian tumors to that of normal ovarian tissue using two published datasets (2, 3). We found that CEPD1 ovarian cancer was cadherin-like and PC esterase domain containing 1, or CPED1 was among the genes most differentially expressed between ovarian cancers and normal ovarian tissue. This finding was conserved across both datasets. Modulation of CPED1 expression should be evaluated for its ability to specifically target the growth of ovarian cancers.

Methods

We used datasets GSE119056 (3) ($n=3$ for control and $n=6$ for tumor) and GSE54388 (4) ($n=6$ for control and $n=16$ for tumor) to perform this analysis using GEO2R. The authors of GSE119506 utilized Agilent 067406 CBC lncRNA + mRNA microarray V4.0 technology to generate the microarray dataset utilized here. The authors of GSE54388 utilized Affymetrix Human Genome U133 Plus 2.0 array technology to generate the microarray dataset also utilized here. The Benjamini and Hochberg method of p-value adjustment was utilized, and p-value adjustment was set to “Auto-detect”. The NCBI generated category of platform annotation was utilized. To evaluate the statistical significance of differences in RNA expression values in control (normal, benign) versus tumor groups, a two-tailed, unpaired t test

with Welch's correction was performed to obtain a p-value. P-values less than 0.05 were considered statistically significant.

Results

We compared the transcriptomes of ovarian tumors and the normal ovary using two published datasets (3, 4) to identify the genes whose expression changes the most between benign and malignant ovarian tissue.

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We found across that both datasets, CPED1 was among the most differentially expressed genes in the ovarian tumor transcriptome. In one group, CPED1 was ranked 157 out of 65534 total transcripts in terms of how much its expression changed (differential expression) between tumor and benign tissue of the ovary (Table 1; $p=8.75E-10$), while in the other group, differential expression of CPED1 was ranked 132 out of 54675 transcripts (Table 1; $p=3.26E-06$).

CPED1 is expressed at significantly lower levels in ovarian tumors than in normal ovarian tissues.

We then obtained the exact mRNA expression values for CPED1 in tumor and control ovarian tissue samples from both datasets. Across both groups of patients (separate datasets), CPED1 was expressed at significantly lower levels in ovarian tumors than in the normal ovary (Figure 1: $p=0.0003$ and $p<0.0001$ for GSE54388 and GSE119056, respectively).

Thus, we identified CPED1 as one of the genes whose expression changed the most significantly between tumors from women with ovarian cancer and normal ovarian tissue, and found that CPED1 was expressed at significantly lower levels in ovarian tumors than in the ovary.

Discussion

Ovarian cancer is the fifth leading cause of cancer death for women in the United States and results in 17,000 deaths each year (2). Standard chemotherapies include platinum drugs and taxanes (3); there are no targeted therapies available for the treatment of ovarian cancer (5). Discernment of the most significant changes in the gene expression between the ovary in health and ovarian tumors can illuminate the fundamentals of transcriptional behavior of ovarian cancers. We performed global differential gene expression profiling of ovarian tumors by comparing the transcriptomes of tumors isolated from two independent groups of patients to the transcriptomes of benign, control ovarian tissue using two published datasets (3, 4). We identified the cadherin-like and PC-esterase domain containing 1 CPED1 as among the most differentially expressed genes in the ovarian cancer transcriptome and found that it was expressed at significantly lower levels in ovarian tumors than in control ovarian tissue.

CEPD1 (also known as C7orf58) contains an acylesterase domain, a second N-terminal beta-sandwich domain with a cadherin-like fold and an ATP-grasp domain fused to the PC-esterase domain. Thus, it belongs to the PC-esterase family derived from the GDSL/SGNH superfamily of esterases including platelet activating factor acetylerase which contain a GDSL motif between the first conserved helix and strand, as well as conserved S, G, N and H residues around the active site of the enzyme (6). One study of alternative splicing of the CPED1 gene showed that CPED was expressed in many tissues but absent from circulating leukocytes (7). CPED1 is highlighted as being a target of microRNA-183 in one study of ovarian cancers (8) but there is no other literature describing a relationship between CPED1 and ovarian cancers. This is the first report of CPED1 differential expression in ovarian tumors and modulation of CPED1 expression by over-expression in xenograft mouse models of ovarian cancer (9) should be performed to assess whether decreased expression of CPED1 is required to support ovarian cancer tumor growth.

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	p-value	t	B	gene	gene name	ID
GSE54388						
132	8.75E-10	-10.1075101	12.589426	CPED1	cadherin like and PC- esterase domain containing 1	228728_at
GSE119056						
157	3.26E-06	-9.0371925	5.01023	CPED1	cadherin like and PC- esterase domain containing 1	NM_024913

Table 1: CPED1 is differentially expressed in ovarian cancer.

The rank of differential expression by dataset analyzed (out of 54675 transcripts (GSE54388) or out of 65534 transcripts (GSE119056)), the p-value of global differential expression, t, a moderated t-statistic, B, the log-odds of differential gene expression between tumor and control groups, the gene, gene name and probe or transcript ID are shown in this chart, provided by GEO2R.

Figure 1: CPED1 is expressed at significantly lower levels in ovarian tumors than in normal ovarian tissues.

The expression of CPED1 in benign ovarian tissues (green) and ovarian cancers (tumor tissues, red) is shown by bar graph with the error bars denoting the standard error of the mean (left), by a violin plot representing minimum to maximum expression with the dotted horizontal line denoting the median value and the finer lines denoting the 25th and 75th percent quartiles of expression (middle), and with dots representing the expression level in each individual patient tumor or control ovary tissue sample, with the horizontal black line representing the mean CPED1 expression value (right). Data from GSE54388 is shown in 1A, while data from GSE119056 is shown in 1B. A statistical test was performed to evaluate the significance of expression between tumor (ovarian cancer) and control (ovary) groups, and the results of those tests, a p-value, is shown on each graph.