PGC1α and VDAC1 expression in endometrial cancer

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Abstract. Endometrial cancer (EC) is one of the ten most common gynecological cancers. As in most cancers, EC tumour progression involves alterations in cellular metabolism and can be associated with, for instance, altered levels of glycolytic enzymes. Mitochondrial functions and proteins are known to serve key roles in tumour metabolism and progression. The transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1 (PGC1α) is a major regulator of mitochondrial biogenesis and function, albeit of varying prognostic value in different cancers. The voltage-dependent anion channel type 1 (VDAC1) regulates apoptosis as well as metabolite import and export over the mitochondrial outer membrane, and is often used for comparative quantification of mitochondrial content. Using immunohistochemistry, the present study examined protein expression levels of PGC1α and VDAC1 in tumour and paired benign tissue samples from 148 patients with EC, in order to examine associations with clinical data, such as stage and grade, Ki-67, p53 status, clinical resistance and overall survival. The expression levels of both PGC1α and VDAC1, as well as a PGC1α downstream effector, were significantly lower in tumor tissues than in benign tissues, suggesting altered mitochondrial function in EC. However, Kaplan-Meier, log rank and Spearman's rank correlation tests revealed that their expression was not correlated with survival and clinical data. Therefore, PGC1α and VDAC1 are not of major prognostic value in EC.

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Introduction

Endometrial cancer (EC) is the leading gynecological malignancy in the Western world, and one of the top ten most common cancers among women (1). Obesity, polycystic ovarian syndrome and nulliparity are risk factors for EC (1-3). The risk of developing EC increases with age and more than 90% of cases present in peri- and postmenopausal women, with a peak incidence in the sixth decade (4). Based on clinical and molecular characteristics, EC is classified into two subgroups. Type 1, also known as endometrioid type, is the more common one, representing ~80% of uterine cancer cases, and is typically hormone sensitive, linked to an excess of estrogen, and has a better prognosis. Type 2, or non-endometrioid type, accounts for 20%, and is typically estrogen independent and comprises sarcomas, clear cell carcinomas and others. Type 2 is more common in senior women and clinically presents as a more aggressive disease with a higher recurrence rate than type 1 (1,5,6).

Since symptoms such as abnormal vaginal bleedings present early, EC is often diagnosed at an early stage, which likely contributes to the favorable prognosis, with overall 5-year survival higher than 80% (6). However, metastasis, chemoresistance and recurrence remain a challenge.

Tumour progression, notably metastasis and chemoresistance, involves changes in cellular metabolism that benefit tumour cell growth and survival; of these changes, the Warburg effect, or high rates of aerobic glycolysis, is perhaps the most well-known (7,8). Alterations in the levels of PKM2, GAPDH and ATP5B, i.e., enzymes related to cellular metabolism, were shown to be associated with the shorter survival in patients with ovarian carcinomas (9). Alterations in mitochondrial functions are instrumental to the metabolic plasticity of tumour cells (10,11), but also to metastasis, as upregulation of mitochondrial oxidative phosphorylation by metastatic cells was linked to superoxide production and subsequent regulation of cell adhesion processes (12).

The transcriptional coactivator peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1 (PGC1α) is important in regulating mitochondrial biogenesis and function, and lower levels of PGC1α expression have

been noted in various cancers, such as breast, colon (13), and ovarian cancers (14). Of note here, PGC1α has been shown to be influenced by the presence of estrogen. Other mechanisms are possible; thus, type 1 EC is reported to harbor mutations in mitochondrial DNA (mtDNA) which affect Complex I, and which might thereby lead to the observed upregulation of mitochondrial biogenesis and PGC1α (15,16). In line with differential regulatory pathways, both increased and decreased levels of PGC1α have been associated with more aggressive cancer and poor prognosis (17).

The voltage-dependent anion channel type 1 (VDAC1) protein located in the outer mitochondrial membrane regulates mitochondrial import and export of ions and metabolites, including Ca^{2+}, ATP and NADH, and thereby regulates oxidative phosphorylation (18). VDAC1 is also involved in regulating cell death through interactions with various proteins including hexokinase (HK), Bcl-2 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (19). VDAC1 is often used as a marker of mitochondrial content of cells (20).

In the present study, we assessed protein expression of PGC1α and VDAC1 in type I and II ECs and paired non-cancerous tissue, in order to examine a putative correlation between them and clinical data such as subtype, stage and grade, clinical resistance and overall survival.

Materials and methods

Patient material. Tumour samples were obtained from 148 patients diagnosed with EC between January 2008 and March 2012 at Karolinska University Hospital, Stockholm. Upon resection of the uterus, approximately 1 cm^3 of the tumour was collected for analysis, along with a sample of normal endometrium. In all, the study included 126 (85%) patients with type I and 22 (15%) patients with type II endometrial adenocarcinoma. In addition, paired benign non-cancerous tissue was obtained from 135 (91%) of these women. Cases were classified into type I and II according to histopathological assessment and further characterized using the International Federation of Gynecology and Obstetrics (FIGO) system into stage, extent of myometrium invasion and grade of endometrial carcinoma. Cases were assessed by the hospital pathology laboratory at the time of diagnosis for hormone receptor status, p53 and ploidy. Tumour characteristics of the total cohort and characteristics, according to subtype, are described in Table I.

Immunohistochemistry and antibodies. Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tumour blocks, as described previously (9). Tumour sections (4 μm) were stained using the Vectastain Elite ABC kit (Vector Laboratories). For antigen retrieval, sections were heated in a microwave oven in citrate buffer for 20 min. Primary antibodies were anti-Ki-67 (M7240, Dako; Agilent Technologies, Inc.; 1:400), anti-PGC1α (ab54481, Abcam; 1:200) and anti-VDAC1 targeting the N-terminus (1-19 amino acids) and the central region (150-250 amino acids) (529532 from Calbiochem, and ab15895 from Abcam, respectively). Slides were incubated with primary antibody for 30 min at room temperature and then with secondary antibody before addition of the avidin-biotinylated peroxidase complex.

Table I. Tumour characteristics (n=148).

Characteristics	No. (%)
Histology	
Endometrial only	125 (84.5)
Serous or mixed	15 (10.1)
Clear cell	7 (4.7)
Stage	
1	103 (69.6)
2	25 (16.9)
3	17 (11.1)
4	3 (2.0)
Grade	
1	39 (26.4)
2	60 (40.5)
3	49 (33.1)
Depth of myometrial invasion	
None	10 (6.8)
<50%	72 (49.0)
≥50%	63 (42.9)
Through the serosa	2 (1.4)
Relapse	25 (16.3)

Evaluation of immunohistochemistry. Two observers (OCW and LL), blinded for clinical outcome, independently evaluated all slides by assessing the whole tumour area or, in the normal tissues, epithelial cells. Positive PGC1α and VDAC1 immunoreactivities were observed, and the percentages of positively stained cells were categorized semiquantitatively from 0 to 3 (0, <1; 1, 1-25; 2, 25-50 and 3, >50%). On the same scale, the maximum staining intensity was scored 0-3 (negative, weak, moderate and strong). Immunoreactivity scores represent the products of the two parameters. The ratio of tumour (T) immunoreactivity score to normal (N) was then calculated. As only 135 (91%) paired normal tissues were available for analysis, the T/N immunoreactivity was trichotomized as T/N <1, T/N=1 or T/N >1. Ki-67 staining was evaluated as percentage of tumour cells with a positive nucleus. Five separate sets of 100 cells were counted, and the average number of positives given as the reported value.

Statistical analysis. We compared the expression of PGC1α and VDAC1 in malignant and benign paired tissue using the Wilcoxon signed rank test. The Wilcoxon test was used on the stratified cohorts in order to compare PGC1α expression at different stages. A P-value <0.05 was set to indicate a statistically significant difference. To assess survival was significantly different between patients with different levels of PGC1α or VDAC1 expression, we used Kaplan-Meier and log rank test. Spearman's rank correlation coefficient was used in order to estimate the correlation between PGC1α, TFAM, p53, respectively, and tumour characteristics. The Kruskal-Wallis test was used for comparing several groups, and the Mann-Whitney U test when there were two groups,

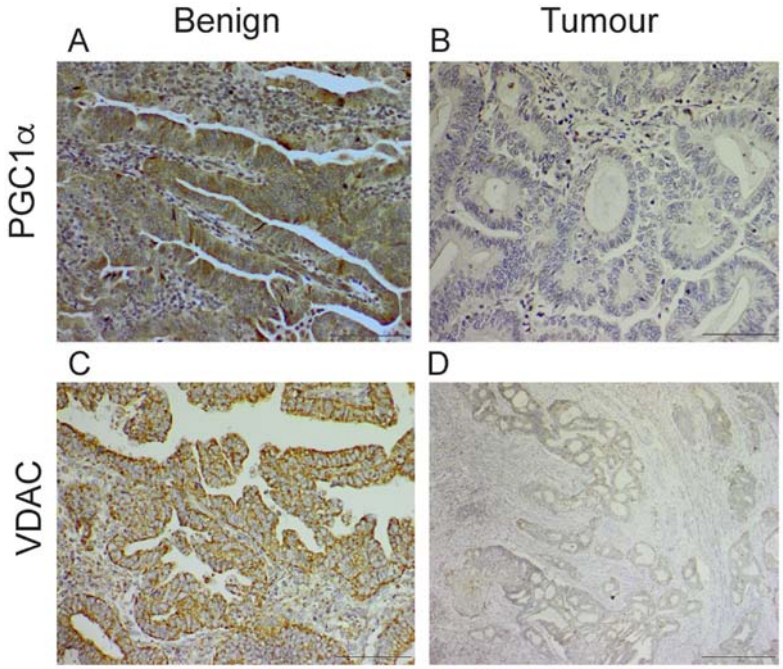

Figure 1. Immunohistochemical staining of PGC1α and VDAC1. The images are representative of high and low expression levels, respectively, of PGC1α and VDAC1 in benign and tumour tissue. (A) PGC1α in benign tissue. (B) PGC1α in tumour tissue. (C) VDAC1 in benign tissue. (D) VDAC1 in tumour tissue. Bars indicate 2 mm. PGC1α, peroxisome proliferator-activated receptor γ coactivator 1; VDAC1, voltage-dependent anion channel type 1.

since there were non-parametric data. Analyses and figures were made using IBM SPSS 25.0 Mac OS.

Ethics. The study obtained ethics approval from the Regional Ethics Committee Stockholm, Sweden, which includes approval of the patient consent process. Registration no. 2010/1536-31/2.

Results

Clinicopathological features of the cohort. Using immunohistochemistry, we analyzed the expression of PGC1α and VDAC in 148 cases of EC, including 126 type I (85%), and 22 type II (15%). Patients' median age at the time of diagnosis was 70.0 (IQR 65.3-77.0), BMI=26.3 (23.7-30.1) and parity=2 (1-3). 44.9% (67/148) of the women were previously prescribed hormone replacement therapy. No significant difference in median age was observed between the subtypes. Tumour characteristics are described in I. Representative images of immunohistochemical staining for PGC1α and VDAC are shown in Fig. 1. As expected, significant differences between subtypes were found for the biomarkers ERα and progesterone. The percentage of Ki67-positive cells, a well-established marker of proliferation (21), was over 20-fold higher in malignant tissue compared to the benign (Fig. 2). Ki67 expression in tumour tissue correlated with a shorter time to relapse (P<0.001).

PGC1α expression in EC. PGC1α expression was found to be significantly decreased in tumour tissue (P=9.2E-19) compared to paired benign tissue (Fig. 3). We also examined one of its downstream effectors, the mitochondrial transcription factor TFAM, and noted a weak, positive correlation between TFAM and PGC1α expression within the malignant tissue, which was statistically significant (r_s=0.378, P=0.016;

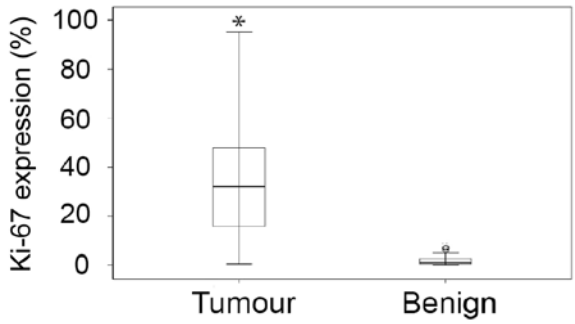

Figure 2. Ki-67 expression. The Ki-67 index, or percentage of tumour cells with a positive nucleus in immunohistochemistry, was significantly higher in tumour cells [31.1 (14.6, 47.9) vs. 1.00 (0.38, 2.60), P<0.0001; Wilcoxon signed rank test]. *P<0.05.

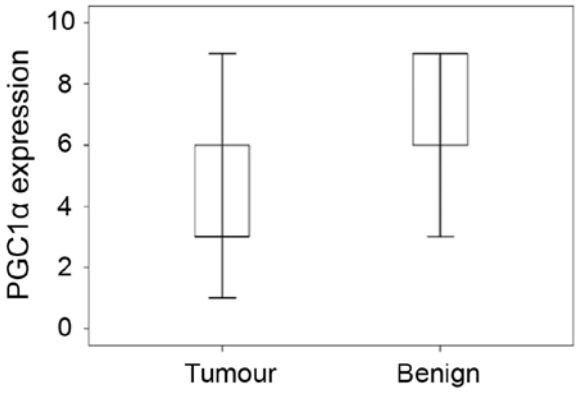

Figure 3. PGC1α expression. Immunohistochemical staining and scoring for PGC1α demonstrated significantly lower expression in tumour than in benign tissue [3.0 (3.0, 6.0) vs. 9.00 (6.00, 9.00); P<0.0001; Wilcoxon signed rank test]. Expression levels (y-axis) are based on the proportion of positive cells and the intensity of staining. PGC1α, peroxisome proliferator-activated receptor γ coactivator 1.

Table II. Associations between tumour characteristics and PGC1α expression in tumour tissue.

Characteristic	Number	PGC1α score, median (IQR 25, 75)	P-value
Invasion			
0	9	4.00 (3.00, 6.00)	0.294
1	73	4.00 (3.00, 6.00)	
2-3	65	3.00 (3.00, 6.00)	
Stage			
1	103	3.00 (3.00, 6.00)	0.773
2	25	6.00 (3.00, 6.00)	
3-4	20	6.00 (3.00, 6.00)	
Grade			
1	39	3.00 (3.00, 6.00)	0.903
2	60	3.50 (3.00, 6.00)	
3	49	6.00 (3.00, 6.00)	
Tumour size[a], mm			
≤30	47	3.50 (3.00, 6.00)	0.090
>30	43	3.00 (3.00, 6.00)	
Histology			
Type I	125	3.00 (3.00, 6.00)	0.113
Type II	22	6.00 (3.00, 6.00)	

[a]Data from the 90/148 samples for which size was documented. PGC1α expression is shown as a semiquantiative score based on the categorization of percentage of positively stained cells and the maximum staining intensity. The Kruskal-Wallis test was used for comparing several groups, and the Mann-Whitney U test for comparing two groups. PGC1α, peroxisome proliferator-activated receptor γ coactivator 1.

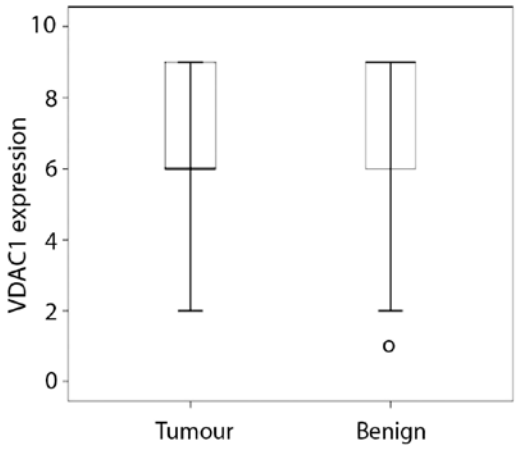

Figure 4. VDAC1 expression. Immunohistochemical staining and scoring for VDAC1 demonstrated significantly lower expression in tumour tissues than in benign tissue [6.0 (6.0, 9.0) vs. 9.00 (6.00, 9.00); P=0.005; Wilcoxon signed rank test]. Expression scores (y-axis) are based on the proportion of positive cells and the intensity of staining. VDAC1, voltage-dependent anion channel type 1.

2-tailed sig.) (Fig. S1). There was also a positive correlation with VDAC expression (r_s=0.310; P<0.0001) (Fig. S2), and a weak one with p53 (r_s=0.2, P=0.016; data not shown).

No association between tumour characteristics (invasivity, stage and grade) and PGC1α expression was found (Table II). There was no significant difference in expression between tumours larger or smaller than 30 mm (P=0.09; Table II). Nor was there any significance with a cutoff of 40 mm (P=0.192). There was no significant difference in expression between type I and II tumours (P=0.113; Mann-Whitney U test). Neither was there any association between expression and relapse or mortality (P=0.345 and 0.758, respectively; Log-rank test). However, we did observe a tendency towards shorter time to death with lower PGC1α expression in grade 1 FIGO patients. Although interesting, this finding was not significant according to ANOVA, probably due to the low number of observations in the groups.

VDAC expression in EC. Expression of VDAC was significantly lower in tumour tissue compared to benign tissue (Fig. 4). Although there was no correlation between VDAC1 and mortality (data not shown), there was a weak correlation between intermediate VDAC1 expression and shorter time to relapse (chi^2=6.81; P=0.03; Log-rank test) (Fig. S3). However, it was non-significant after adjustment for age (data not shown).

Discussion

Tumour pathogenesis and progression go hand in hand with major metabolic alterations, notably altered mitochondrial function(s) (22). The transcriptional coactivator PGC1α is well-studied, particularly in normal tissue, as a major regulator of mitochondrial biogenesis and function, and is generally perceived to promote an oxidative metabolism (13). Regarding its role in cancer and as a prognostic marker, reports vary greatly, as both high and low levels have been found to correlate with worse outcome (17). Here, we studied the expression of PGC1α in EC. The main findings were

that its expression was lower in cancer tissue than in benign tissue from the same patient and that there was no correlation between the expression of PGC1α and aggressive course of the disease. We also examined the expression of VDAC located in the mitochondrial outer membrane and which regulates mitochondrial import and export of ions and metabolites. VDAC expression was lower in the tumour tissue than in benign tissue. In agreement with the current understanding of Ki67 as a cellular marker for proliferation, we observed significantly higher Ki67 expression in tumour tissue than in adjacent benign tissue, and an association with shorter time to relapse. Others have shown that survival in EC patients is independently influenced by Ki67 expression (23).

That the decreased expression of PGC1α in EC tissue was similar in the two subtypes of EC was perhaps unexpected considering that type I is estrogen sensitive and that a model for how hyperestrogenism promotes EC progression involving PGC1α has been proposed (24). Moreover, the results contradict those of Ren *et al* (25) who reported increased PGC1α expression in a small (n=15) cohort of EC type I tumours; however, these were compared to benign tissue from healthy controls, and data were on mRNA rather than the actual protein. In a larger study comparing EC tissue to benign, Cormio *et al* (16) reported doubled levels of PGC1α and of the mitochondrial transcription factor TFAM which is known to be in part regulated by PGC1α (13). An important difference between their study and the present one is that they assessed protein expression levels by western blotting, i.e., in heterogeneous extracts, whereas we evaluated it specifically in cancer cells.

Similar to our results, others have reported decreased expression of PGC1α in, for instance, colon (26), breast (27) and clear-cell ovarian cancer (14). Furthermore, other studies have associated a decrease in the expression of PGC1α with poor prognosis in human breast cancer and hepatocellular carcinoma (13). By contrast, we could not find any overall correlation in EC between PGC1α expression and prognosis. However, there was a tendency that among grade 1 patients, the lower expression could be associated with a shorter time to death. This tendency, which needs to be confirmed, supports the notion of a context-dependent protective function of PGC1α (17). A recent example of the same is the finding that decreased PGC1α expression may contribute to tumour invasion and metastasis (28).

VDAC expression is often used as a marker of mitochondrial content. In line with downregulation of PGC1α and a putative downregulation of mitobiogenesis, VDAC expression was also decreased in both type I and II EC tumour cells compared to benign tissue. However, its expression has been reported to vary in cancer cells (20,29). Likewise, we have noted VDAC upregulation also in the absence of PGC1α expression in ovarian clear cell carcinoma (14), a subtype that is notoriously resistant to treatment. Altogether, this supports the idea that VDAC is not necessarily a 'housekeeping' indicator of mitochondrial content, and we therefore suggest that the roles and functions of VDAC in tumour cells depend on cellular context.

Our data are based on a large and representative group of patients. Importantly, each patient is her own control, as we used paired tumour and benign tissue samples from the same patients, and thus did not have to create a matching control group. On the other hand, it is impossible to exclude the risk that the healthy tissue adjacent to cancer tissue does not harbour some pre-cancerous molecular changes.

Further investigation of the correlation between lower PGC1α expression and shorter time-to-death, in particular in the FIGO Grade 1 group, could be of clinical significance. If expression of PGC1α at early cancer stages is correlated with a higher risk of recurrence it might thus signal that these patients be treated more aggressively than is generally the case today.

In summary, we have shown downregulation of PGC1α as well as VDAC protein levels in EC of both types, indicating altered mitochondrial functions in EC compared to benign tissue. The results also indicate that PGC1α and VDAC levels are not of major prognostic value in EC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

OCW and LL scored the stained slides, structured all data and wrote manuscript drafts. IG performed statistical analyses and contributed to the final manuscript. MM wrote the ethical approval application and collected the tissue samples and clinical data. MG organized lab work and immunohistochemistry and contributed to the overall design. MS conceived the study and finalized the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Regional Ethics Committee of Stockholm, Sweden, and this includes approval of the patient consent process. Both oral and written consent was received in conjunction with consultation with a clinician. Registration number 2010/1536-31/2.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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