Dysregulated TCA Cycle Pathway in Endometrial Cancer

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Abstract: Background: Numerous questions regarding metabolism alterations in endometrial cancer remain unanswered. Methods: We used the Mann-Whitney test to identify significantly downregulated genes in Cluster II, which were then subject to Ingenuity Pathway Analysis and Gene Ontology (GO) enrichment analysis. We next compared the expression levels of several key enzymes between the CTNNB1 mutant and wide-type patients to correlate “TCA Cycle” alterations with CTNNB1 mutation status. Finally, we performed a Spearman correlation between the TCA Cycle genes and the immune checkpoint molecule to understand the relationship between TCA Cycle dysfunction and immune response. All statistical tests were two-sided. Results: A total of 603 genes were significantly downregulated in Cluster II. Pathway analysis showed that metabolic pathways were frequently dysregulated, and GO analysis demonstrated that metabolic processes were commonly retarded. In particular, TCA Cycle is the most significantly altered metabolic pathway ($P = 1.45 \times 10^{-7}$), with one-third of the enzymes altered. The TCA Cycle pathway activity and the expression levels of several key enzymes were significantly lower in CTNNB1 mutant patients, compared to CTNNB1 wide-type patients. In addition, the TCA Cycle pathway activity and the expression levels of pathway genes were significantly and positively correlated with PD-L1 gene expression. Conclusion: This study systematically characterizes a subset of endometrioid endometrial cancer patients with dysregulated TCA Cycle pathway, which may contribute to immune resistance in endometrial cancer.

Keywords: TCA cycle; metabolism; CTNNB1 mutation; immune response; endometrial cancer

Received: 28th March 2019; Accepted: 13th May 2019; Published Online: 16th May 2019

1. Introduction

The “Warburg effect” is a well-known phenomenon in cancer cells that produce energy mainly through glycolysis, instead of oxidative phosphorylation[1]. The shift to a glycolytic phenotype and increased glucose uptake are characteristics of cancerous cells, and intrinsically associated with signaling pathways and oncogenic transformation. This glycolytic switch is reported to be promoted by the PI3K/Akt pathway[2], Myc overexpression[3], p53 inaction[4], and HIF-1α stabilization[5]. Abnormalities of the glycolytic process in cancer cells have significant impact on other metabolic pathways and biological processes. The product of glycolysis either enters the Krebs cycles or is excreted as lactate, while the glycolytic intermediates are used for synthesis of fatty acids and non-essential amino acids, promoting lipid biosynthesis. Glucose is also used to generate nucleic acids via the pentose phosphate pathway[6]. An acidic environment created by glycolysis was reported to suppress anticancer immune effectors[7], such that lactate inhibited the cytolytic activity of cytotoxic T lymphocyte by suppressing the cytokine production.

Endometrial carcinoma (EC) is a common gynecological cancer with approximately 63,230 new cases and...
11,350 deaths estimated in the United States in 2018. Obesity, which is a major risk factor for sex steroid hormone production and insulin resistance, is a contributor to the increasing incidence of EC. The link between obesity and endometrial cancer also suggests the important role of metabolism in EC carcinogenesis. Consequently, metabolic alterations in endometrial cancer have attracted a large amount of interest in recent years. Compared to normal endometrium, endometrioid carcinoma exhibits a distinct pattern in metabolic profiling that is associated with increased glycolysis/lipogenesis and decreased glucose oxidation. In vitro study has demonstrated that high glucose conditions have led to increased cell proliferation, colony formation, and an increase in glycolytic activity, along with increased glucose uptake. The endocannabinoid system has been reported as a potential pathway involved in EC pathogenesis, and purine metabolism may be involved in tumor myometrial invasion. PGC-1α and ERRγ were involved in energy metabolism and contributed to endometrial cancer development. Deregulated choline biochemistry, due to increased expression of choline kinase alpha, is strongly indicative of endometrial cancer pathogenesis.

Nevertheless, numerous questions still remain unanswered. For instance, is there a specific metabolic profile that is unique in a subset of endometrial cancer patients and different from other patients? Is this particular metabolic profiling associated with known oncogenic mutations? Is there any relationship between this metabolic profiling with immune profiling? We previously analyzed gene expression profiling and identified four molecular subtypes (I – IV) in endometrioid-type endometrial cancer (EEC) with distinct molecular and clinical characteristics. Cluster II with low-grade disease, but poor survival was characterized by CTNNB1 gene mutations. In addition to Wnt pathway activation, which was the focus of our previous report, we hypothesize that this subset of patients also had deregulated metabolic pathways, in particular the TCA Cycle pathway. In the present study, we performed comprehensive characterization of Cluster II tumors via integrated genomic analyses. Our results show that genes in the TCA Cycle pathway were significantly downregulated in Cluster II tumors. The expression levels of the TCA Cycle pathway genes, along with pathway activity, are significantly associated with CTNNB1 mutation status. Finally we examined the relationship between the TCA Cycle profile and the immune response that was evaluated by PD-L1 gene expression.

2. Methods
2.1 Patient Samples
RNA-sequencing expression profiling, CTNNB1/TP53 mutations, and body mass index (BMI) data from a total of 271 EEC patients, along with molecular subtyping, were obtained from The Cancer Genome Atlas (TCGA) database. We obtained the molecular subtype data for these patients from our recent work, among which 78 cases were in Cluster I, 61 in Cluster II, 72 in Cluster III and 60 in Cluster IV. Access to the TCGA database was approved by the National Cancer Institute. MD Anderson Cancer Center waived the requirement for ethical approval of this analysis, because the registry contains only de-identified data. Written consent was obtained from all living patients.

2.2 Gene Expression and Pathway Analysis
To identify genes that were significantly dysregulated in Cluster II, we compared Cluster II with the other three clusters combined, and then compared Cluster II with the other individual clusters in a pairwise manner with the use of Mann-Whitney test. We provided both fold change (FC) and test statistic (P value) for all of these analyses. The downregulated gene signature was then selected such that FC < 0 and P value < 0.01 for all comparisons. Ingenuity Pathway Analysis (IPA) was then applied to identify metabolic pathway enrichment. We used the Ingenuity Knowledge Base, which includes all genes, as a reference set, and then determined statistical significance using Fisher’s exact test. Of note, the pathways with a small number of genes (< 10 genes) are not shown.

2.3 Gene Ontology Enrichment Analysis
Using the publicly available tool (http://gencodeontology.org), we performed Gene Ontology (GO) enrichment analysis on the dysregulated gene signature to identify the over-represented annotation terms associated with particular biological properties. The GO database, released in October 2018, is used for the annotation set and the whole-genome Homo sapiens genes are used as a reference list. Fisher’s exact test was used to assess statistical significance. Of note, we only exported the most specific annotations, and the corresponding parent terms were excluded. The GO terms were sorted by FCs of enrichment.

2.4 TCA Cycle Pathway Score
We previously devised an mRNA metric to charac-
terize the TGF-β pathway activity. Using a similar approach, we calculated the TCA Cycle pathway score in this study to quantify activities of this metabolic pathway. In brief, we used the eight genes that were involved in the TCA Cycle pathway and significantly downregulated in Cluster II to calculate the pathway score. We first calculated the z score of each of the eight genes across all the samples, and then took the median of all gene z scores for each sample as the TCA Cycle pathway score. The pathway score served as a means of assessing the overall level of TCA Cycle pathway activity and was less susceptible to the expression variations of individual genes.

2.5 Gene Set Enrichment Analysis

Gene set enrichment analysis (GSEA) was performed to determine whether the TCA Cycle showed statistically significant association with the CTNNB1 mutation phenotype. Genes were ranked in descending order on the basis of signal-to-noise ratios of genes, comparing CTNNB1 wide-type patients with CTNNB1 mutant patients. The enrichment score was calculated by walking down the ranked gene list; it increased when a gene was in the pre-defined gene set, and decreased when it was not.

2.6 Statistical Analysis

Mann-Whitney test was performed to evaluate the statistical differences in expression levels of enzymes of the TCA Cycle pathway for CTNNB1 mutant versus wide-type patients. The Spearman correlation test was used to examine the expression association between the immune checkpoint molecule versus the TCA Cycle

Figure 1. Metabolic pathways are frequently altered in Cluster II endometrial cancer patients. A) Identification of significantly downregulated genes in Cluster II. Patients (column) are ordered by molecular subtyping. CTNNB1/TP53 gene mutations and body mass index (BMI) for each individual patient are also shown. The BMI data for the Cluster II patients are highlighted in red and for other patients in black. B) Significantly enriched metabolic pathways in the downregulated signature genes are shown in panel A. X-axis in the left panel denotes P-value in the -log10 scale. The right panel shows the ratio of genes that are included, both in the pathway and in the downregulated gene set, to the overall genes that are included in the pathway. The total number of genes that are included in the pathway is indicated in the parenthesis.
pathway genes. Statistical significance for both pathway analysis and GO enrichment analysis was assessed via Fisher’s exact test. All tests were two-sided, and statistical significance was defined as $P < 0.05$. Note that the $P$ values were not corrected for multiple testing and the significance was presented mainly for purposes of hypothesis generation, instead of for formal inference. Analyses were primarily performed using the scientific software Matlab, version 8.4 (MathWorks, Inc., Natick, MA), SPSS version 18 (SPSS Inc., Chicago, IL), and GraphPad Prism, version 6 (GraphPad Software, Inc., La Jolla, CA).

3. Results

3.1 Metabolic Pathways are Frequently Altered in Cluster II Endometrial Cancer Patients

We recently identified four clinically-relevant molecular clusters in ECC$^{[16]}$. Cluster II was comprised of younger, obese EEC patients with low-grade and low-stage disease; however, this subset of patients likely recurred and had a poor survival$^{[16,21,22]}$. In addition to Wnt/β-catenin and epithelial-mesenchymal transition (EMT) pathway activation, several Sulfate Biosynthesis pathways involving genes (such as SULT1C4, CHST11, HS3ST1, CSGALNACT1, CHST15, ACSL5, ACSL4, RBP1, and DIO2) were also significantly upregulated in Cluster II patients. In addition, Cluster II patients had a higher BMI, though not statistically significant (averaging 36.54 for Cluster II patients versus 33.84 for the other patients, $P = 0.083$, Mann-Whitney test, Figure 1A). Collectively, these data indicated that Cluster II was likely implicated with metabolism dysfunctions. To obtain a comprehensive view of metabolic alterations in the downregulated direction, we performed a significance analysis for gene expression profiling and identified a total of 603 genes that were significantly

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<th>Go terms</th>
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<th>Gene list $^b$</th>
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<th>FE $^c$</th>
<th>$P$-value</th>
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$^a$ this column shows the number of genes annotated to a GO term in the reference list (background set);  
$^b$ this column shows the number of genes annotated to a GO term in the downregulated gene list (as shown in Figure 1A);  
$^c$ FE = fold enrichment.  
The processes highlighted in blue are related to metabolism.
downregulated in this clusters (see Methods for details) (Figure 1A). Pathway analysis of these downregulated genes shows that metabolic pathways are frequently altered and significantly enriched (Figure 1B). The top eight most significantly enriched metabolic pathways were explicitly listed and over 10% of the genes in most pathways were significantly downregulated (Figure 1B).

To further corroborate these results, we performed a GO enrichment analysis on the significantly downregulated genes. The results only included the most specific subclass, while the parent terms were not shown. The GO terms were sorted by fold Enrichment (Table 1). The statistical significance was assessed by Fisher’s exact test, with the Bonferroni correction for multiple testing. The biological processes pertaining to cellular metabolism were highlighted in blue and top ranked in the list. In line with the pathway analysis (Figure 1B), The GO: 0006099 term (tricarboxylic acid cycle) had the highest fold enrichment of about 10.97, with a $P$ value of about 3.43x10^{-4}. This result further supports the findings from the pathway analysis. The GO: 0009062 term (fatty acid catabolic process) referred to the breakdown of the aliphatic monocarboxylic acids and was the second ranked biological process. The Oxidative Phosphorylation pathway was the second most enriched metabolic pathway (4.26x10^{-5}, Figure 1B). Consistently, the electron transport chain process (GO: 0022900) was third ranked biological process (Table 1). Taken together, these data suggested that metabolic processes were significantly retarded in Cluster II patients.

3.2 TCA Cycle is Significantly Downregulated in Cluster II

As stated above, the TCA Cycle pathway was the most significantly enriched metabolic pathway ($P = 1.45 \times 10^{-07}$, Figure 1B). At the same time, the GO: 0006099 term (tricarboxylic acid cycle) was the top-ranked biological process that was significantly enriched in the downregulated genes (Table 1). To better understand this metabolic pathway, we obtained the schematic of the TCA Cycle pathway from the Ingenuity Pathway Analysis tool (Figure 2A). The green nodes with purple borders represented the genes that were significantly downregulated in this clusters (see Methods for details) (Figure 1A). Pathway analysis of these downregulated genes shows that metabolic pathways are frequently altered and significantly enriched (Figure 1B). The top eight most significantly enriched metabolic pathways were explicitly listed and over 10% of the genes in most pathways were significantly downregulated (Figure 1B).

![TCA Cycle](image1.png)

**Figure 2.** TCA Cycle is significantly downregulated in Cluster II. A) Schematic of the TCA Cycle metabolic pathway. The green nodes with magenta borders represent the significantly downregulated gene complexes. Also shown are the specifically altered genes included in the complexes (in green text). The white oval nodes represent the unchanged genes or gene complexes. The other nodes indicate the intermediate metabolites. B) The TCA Cycle pathway activity assessed by the pathway score was significantly lower in the Cluster II patients than in the other patients ($P < 2.0 \times 10^{-10}$, Mann-Whitney test). In the bar-and-whiskers plots, the box-plot elements are defined as: center line, median; box limits, upper and lower quartiles; whiskers, 1.5 x interquartile range; and points, outliers.
dysregulated in Cluster II patients. The other genes or gene complexes, indicated in white nodes, were involved in this pathway and not included in the downregulated gene list. A total of 24 genes were involved in this pathway, and about one-third of them were significantly downregulated. The whole cycle consisted of nine chemical reactions, and five of them had at least one significantly dysregulated enzyme. Using a similar approach to the one we used for the TCGA TGFβ pathway project\(^1\), we calculated the TCA Cycle pathway score (which can characterize the pathway activity) and compared it between Cluster II patients and the others. The results showed that patients in Cluster II had significantly lower TCA Cycle pathway scores ($P < 2.0 \times 10^{-10}$, Mann Whitney test, Figure 2B), suggesting that the TCA Cycle pathway activity was significantly retarded in these patients.

3.3 TCA Cycle Downregulation is Associated with β-catenin Mutations

Our recent study demonstrated that Cluster II was significantly enriched with $CTNNB1$ gene (encoding β-catenin protein) mutations\(^1\). Given that TCA Cycle was also significantly downregulated in Cluster II, we next sought to examine the relationship between the TCA Cycle alteration and $CTNNB1$ mutation status. When integrating RNA-sequencing and whole-exome sequencing data, we obtained 192 EEC patients who had both gene expression and mutation data, where 63 patients had exon 3 $CTNNB1$ mutations and the remaining samples were considered as $CTNNB1$ wild-type patients (including those with outside exon 3 $CTNNB1$ mutations). To examine the association, we carried out two different analyses. First, we compared TCA Cycle pathway activity, as well as expression levels of the genes as shown in Figure 2A between $CTNNB1$ mutant (mut) group versus $CTNNB1$ wide-type (WT) group with the use of Mann-Whitney test (Figure 3A). The TCA Cycle pathway score was significantly lower in the $CTNNB1$ mut patients than in the $CTNNB1$ WT patients ($P = 0.003$, Mann-Whitney test). Except for $SUCL2$, the other seven genes, including $SDHA$ ($P = 0.002$), $SDHB$ ($P = 0.018$), $SDHD$ ($P = 0.001$), $SUCLG1$ ($P = 0.0005$), $DLD$ ($P = 0.033$), $IDH3A$ ($P = 0.002$), and $ACO1$ ($P = 0.006$), were all significantly lower in the $CTNNB1$ mutant patients. Secondly, we performed a gene set enrichment analysis (GSEA) of the genes between the $CTNNB1$ wide-type and $CTNNB1$ mutant patients, revealing the pathways that were significantly associated with $CTNNB1$ mutation status. Consistently, the KEGG_Citrate_Cycle_TCA_Cycle pathway was the most significantly enriched pathway in genes that were downregulated in the $CTNNB1$ mutant patients (nominal $P = 0.008$), with an enrichment score of over 0.70 (Figure 3B). In all, our data indicated that TCA Cycle downregulation is significantly associated with β-catenin mutations.

3.4 TCA Cycle Alteration is Associated with immune Response

To interrogate the association of TCA Cycle alteration with immune response in endometrial cancer, we next performed a Spearman correlation of both TCA Cycle pathway activity and the expression levels of pathway genes with the expression level of immune checkpoint molecule, PD-L1 (Figure 4). Overall, the
expression level of PD-L1 in Cluster II, indicated by the green dots in the figure, was relatively lower. Lower expression of the immune checkpoint molecules, such as PD-L1, suggests that this subset of patients likely are resistant to immune checkpoint inhibitor therapy. Interestingly, the TCA Cycle pathway score was significantly and positively correlated with PD-L1 gene expression (Spearman rho = 0.323, P = 5.10 x 10^{-08}). In addition, PD-L1 expression was significantly correlated with the expression levels of those genes that were involved in the TCA Cycle pathway, including SDHA (rho = 0.232, P = 1.15 x 10^{-06}), SDHB (rho = 0.267, P = 8.03 x 10^{-06}), SDHD (rho = 0.302, P = 4.08 x 10^{-06}), SUCLA2 (rho = 0.249, P = 3.38 x 10^{-05}), SUCLG1 (rho = 0.138, P = 0.023), DLD (rho = 0.331, P = 2.34 x 10^{-08}), IDH3A (rho = 0.258, P = 1.72 x 10^{-05}), and ACO1 (rho = 0.275, P = 4.30 x 10^{-06}). These data suggest that the TCA Cycle downregulation in Cluster II may partially contribute to immunotherapy resistance for this group of patients.

**4. Discussion**

In this study, we have demonstrated through in-depth statistical analysis of gene expression profiling that metabolic processes are frequently altered in Cluster II, one of the discovered subtypes in our previous study\(^\text{[16]}\). In particular, the TCA Cycle was the most significantly dysregulated metabolic pathway, and significantly associated with CTNNB1 gene mutations and immune response in endometrial cancer. Our study may facilitate identification of an alternative approach to improve cancer immunotherapy by reprogramming the metabol-
ic pathways.

The TCA Cycle dysfunctions have been previously reported to be linked to carcinogenesis in a wide array of cancer types. Mutations in isocitrate dehydrogenase genes (IDH1 and IDH2) reprogrammed the TCA Cycle pathway and produced an oncometabolite known as 2-hydroxy-glutarate from α-ketoglutarate. As a consequence, IDH1 and IDH2 mutations are intimately linked to oncogenesis in glioma and acute myeloid leukemia. Fumarate hydratase (FH) is another important enzyme in the TCA Cycle pathway, which is reported to be mutated in renal cancer; loss of this enzyme exhibited synthetic lethality to cancer cells together with inhibition of haem oxygenation. In the present study, we found that several SDH subunits (i.e., SDHA, SDHB, and SDHD) were significantly downregulated in Cluster II, and expression levels of these subunits were significantly correlated with immune checkpoint expression. SDH deficiency and germline SDH mutations have been identified in several cancer types, including gastrointestinal stromal tumors (GISTs), hereditary paragangliomas and adrenal gland phaeochromocytomas. It has been previously reported that germline SDH and FH mutations decreased their protein expression, and thus resulted in succinate and fumarate accumulation. In addition to mutations of enzymes, the TCA Cycle process can be retarded by reducing the flow of pyruvate into the cycle or due to downregulation of pathway genes, as evidenced in the current study. ACO1 and ACO2 are essential enzymes of the TCA Cycle, catalyzing production and secretion of citrate. ACO2 was significantly decreased in gastric cancer and a lower ACO2 level was associated with increased aggressiveness and poor prognosis. Similarly, we found from this study that ACO1 mRNA expression was significantly lower in Cluster II patients that had poor survival. Similar to this finding is that IDH3A, another downregulated enzyme in Cluster II, was previously reported to activate HIF-1α expression and be associated with prognosis in various cancer types.

Concordant enrichment of TCA Cycle dysfunction and β-catenin mutations in the same set of EEC patients (Cluster II) implied that TCA Cycle alterations may be driven by β-catenin mutations. Indeed, we observed the expression levels of several key enzymes of the TCA Cycle, along with the pathway activity, were significantly correlated with β-catenin mutations, which was consistent with a prior report that mitochondrial TCA cycle impairment was observed in β-catenin-deficient hepatocytes. On the other hand, we observed no significant difference in the glycolysis pathway between β-catenin mutant and wide-type patients. This is also consistent with the previous report. It was reported that β-catenin wide-type and knockout mice exhibited similar levels of pyruvate (the major end-product of glycolysis) and glycolytic gene expression. These data indicate that β-catenin mutations do not impair glycolysis. Rather, β-catenin has been reported to regulate hepatic glucose metabolism through enhancing production of glucose.

There are a few limitations associated with this study. Functional verification of the results is required to infer causality. Measurement of pathway members at the protein levels or intermediate metabolites, such as succinate, is necessary to confirm the TCA Cycle dysfunctions.

5. Conclusions

In summary, our study systematically characterizes the tumor metabolism in endometrial cancer and reports dysfunctions of a particular metabolic pathway in a well-defined subset of EEC patients. Intervention of this pathway may improve the immune response of these patients to the currently emerging immune checkpoint inhibitor therapy.

Acknowledgments

We thank Jessica Swann in the Department of Biostatistics at MD Anderson Cancer Center for editing this manuscript.

Funding

This study was partially supported by grants from the National Institutes of Health/National Cancer Institute: a Developmental Research Award from the MD Anderson Gynecologic SPORE in Uterine Cancers (to YL), the MD Anderson Institutional Research Grant (to YL), and the Mary K. Chapman Foundation.

References


