Reconfiguration of Lipid Metabolism and SCAP-SREBP Pathway in Endometrial Carcinoma

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ABSTRACT

Endometrial cancer (EC), a leading malignancy in women, has seen rising incidence and decreasing age of onset globally, turning it into a significant health concern. Postmenopausal uterine bleeding is a key early sign, enabling prompt diagnosis. EC risk factors include hormonal influences, metabolic disorders, and genetic predispositions. Recent studies have unveiled the vital role of fatty acid metabolism reprogramming in cancer initiation and progression. This research focuses on the gene expression of lipogenesis-related molecules –SREBP cleavage-activating proteins (SCAP), Sterol Regulatory Element Binding Protein (SREBP), Stearoyl-CoA Desaturase (SCD), and Fatty Acid Synthase (FASN)– in endometrial cancer tissues. Using real-time PCR, we analyzed 54 EC patients and 36 healthy controls. The results reveal a significant upregulation of SCAP, SREBPF1, FASN, and SCD in cancerous tissues compared to controls ($p< 0.05$). Additionally, FASN ($p= 0.014$) and SCD ($p= 0.0001$) expression levels were markedly higher in the proliferative phase of controls. These findings highlight the reprogramming of lipid metabolism as a critical driver in EC progression. A deeper understanding of these metabolic pathways could lead to innovative therapies, making lipid metabolism a promising target for future cancer treatments.

Keywords: Endometrial cancer, SCAP, SREBP, FASN, SCD

INTRODUCTION

Endometrial cancer (EC) is the second most frequent gynecologic cancer in women globally and is the sixth most prevalent carcinoma.[1,2] Postmenopausal bleeding is the most common initial sign of EC and usually ensures early diagnosis.[3] According to histopathology, EC is divided into two categories; type I and type II.[4,5] In type I, estrogen plays a more significant role and typically leads to a more favorable outcome, whereas in type II, estrogen does not play a substantial role, resulting in a more challenging clinical course.[1] The tumor is graded by the International Federation of Gynecology and Obstetrics (FIGO) based on the level of glandular differentiation.[1] Tumors in grade 1 have solid nonglandular, nonsquamous growth of less than 5%, whereas those in grade 2 range from 6% to 50% and those in grade 3 exhibit changes exceeding 50%.[3,6]

Metabolic disorders such as obesity, high-calorie diets and sedentary lifestyles are the most prominent risk factors for EC.[7] Reprogramming of lipid metabolism is crucial to the pathophysiology of EC, and the regulation of these metabolic pathways directly impacts energy production, proliferation, and metastasis of cancer cells.[8]

Through fat metabolism, cells obtain signaling molecules essential for energy production, proliferation, survival, invasion, metastasis, and tumor progression, as well as the response to cancer therapy.[2,9] Many malignancies exihibit elevated expression of proteins and enzymes related to lipid intake, storage, and metabolism. Furthermore, cancer cells produce lipids more rapidly than healthy cells by upregulating the expression and activity of key enzymes in their biosynthetic pathways.[9,10]

Endometrial cancer has been increasing in recent years due to high-fat, high-calorie diets and sedentary lifestyles.[2,11] Among all malignancies, EC has the strongest association with obesity.[2,12] Therefore, a better understanding of the regulation mechanism of EC in lipid metabolism will help to develop better therapeutic strategies and methods.[1] Studies indicate that fatty acid synthase (FASN) and stearoyl-CoA desaturase-1 (SCD1) play pivotal roles in the regulation of metabolic and signaling pathways underpinning the biochemical and biological phenotype of EC cells. Targeting these molecules holds potential for the development of novel cancer therapeutics.[13] FASN is a critical enzyme that accelerates fatty acid synthesis in cancer cells. It is highly expressed in numerous malignancies, including EC, where increased FASN expression meets the high energy demands of cancer cells, supporting their proliferation.[14] Furthermore, the enzyme stearoyl-CoA desaturase (SCD) regulates cell membrane dynamics by converting saturated fatty acids into monounsaturated fatty acids. This process promotes cellular proliferation by increasing cell membrane fluidity, especially in cancer cells.[15]

Re-regulation of lipid metabolism is a critical adaptation for the survival and growth of cancer cells. A key molecule in this process is sterol regulatory element binding proteins (SREBPs) and their activator SCAP (SREBP cleavage activating protein).[16] SREBPs initially exist as inactive precursors associated with the endoplasmic reticulum (ER).[17] There are three primary SREBPs: SREBP1a and SREBP1c, which are encoded by the SREBPF1 gene, and SREBP2, encoded by the SREBPF2 gene. Specifically, SREBP-2 controls cholesterol synthesis, SREBP-1c controls the production of fatty acids, and SREBP-1a oversees both processes.[17] The de novo lipogenesis pathway is regulated by SREBP-1, which controls the expression of its enzymes and serves as the key transcription factor for lipogenesis.[16] Activated through SREBP cleavage-activating proteins (SCAPs).[18] SREBPs are essential transcription factors that control lipogenesis and cholesterol biosynthesis, and activation of this pathway in cancer cells is associated with increased production of lipids that promote tumor development.[19] SCAP is an important molecule that activates SREBPs and SCAP-mediated transport of SREBPs to the nucleus accelerates fatty acid biosynthesis in cancer cells.[20]

The aim of our study was to investigate the roles of SCAP, SREBP, FASN and SCD genes in endometrial cancer development and progression, to elucidate the effects of these genes on lipid metabolism and to investigate how targeting these molecules may contribute to new therapeutic strategies. Inhibition of the SCAP-SREBP axis and FASN and SCD, which direct lipogenesis, may be effective in the treatment of EC and these genes are thought to offer important therapeutic targets in cancer biology.

MATERIALS AND METHODS

Tissue samples collected between 01.01.2018-01.01.2023, as Formalin-fixed paraffin-embedded (FFPE) specimens, were included in the study. These samples were obtained from the endometrial tissues of women who underwent hysterectomy and diagnosed with endometrioid adenocarcinoma at the outpatient clinic of the Department of Obstetrics and Gynecology, Mersin University Faculty of Medicine. The patient group consisted of grade I, grade II, and grade III endometrioid adenocarcinoma tissues, while endometrial tissues from healthy individuals in the proliferative and secretory phases were used as the control group. Women under 18 years of age and samples from women with gynecologic conditions other than endometrioid adenocarcinoma were excluded from the study.

The patient population comprised three subgroups, whereas the control population included two subgroups. Samples from 54 patients diagnosed with endometrioid adenocarcinoma were grouped ac-

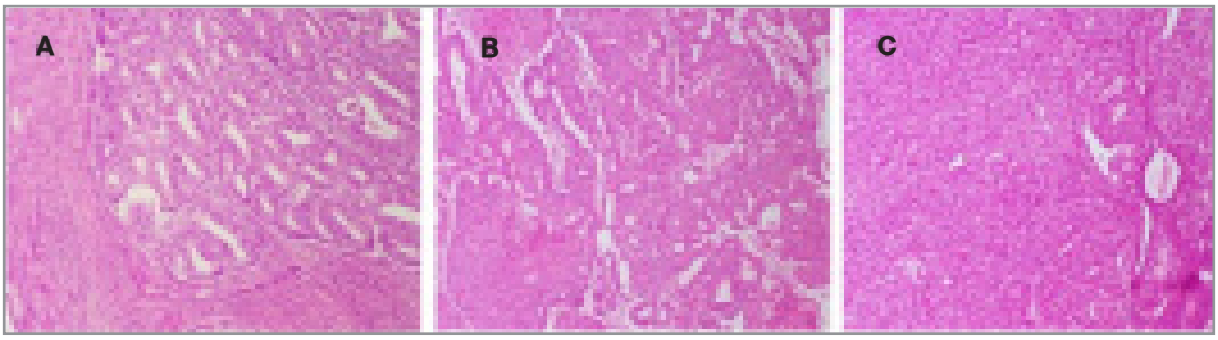

Figure 1. H&E stained preparations of histologically graded endometrioid carcinoma. **A**. Grade 1 (x100), **B.** Grade 2 (x100), **C.** Grade 3 (x100)

cording to Grade 1 (n= 17), Grade 2 (n= 19), Grade 3 (n= 18) and 36 samples from healthy individuals were grouped according to Secretory Phase (n= 20) and Proliferative Phase (n= 16).

All tissue sample series are connected to extensive clinical, histologic, and molecular data.

All Hematoxylin-Eosin (H&E) stained slides of resected tumor materials were examined. Suitable regions on the slides, free of follow-up detection artifacts and with minimal or no necrosis, were identified under a light microscope. Paraffin blocks corresponding to these marked areas were then extracted. Sections measuring 4 mm in diameter and 10 μm in thickness were cut from the newly prepared blocks using a microtome and transferred onto clean slides (Figure 1).

The amount of sample to be transferred to Ependorf tubes was determined according to the protocol of the kit used in the study (IST InnuScreen 845-KS-2050050 innuPREP FFPE total RNA Kit, 50 Assays). Afterwards, deparaffinization of the samples and RNA isolation from the samples were performed. High-Capacity cDNA Reverse Transcription Kit (Thermo Cat. No: 4368814) was used to convert the RNAs we obtained into complementary DNA.

For the primer design of the genes included in the study, the appropriate gene symbols found in the National Center for Biotechnology Information (NCBI, https://www.ncbi.nlm.nih.gov/) were used and studied with SYBR Green dye.

SCAP (F: TTGTGCTGCGCGGCCACCTCA, R: AGGAGGAAAGGGCAGCCGCAC)

SREBPF1 (F: GCTGCTGACCGACATCGAA, R: GGGTGGGTCAAATAGGCCAG)

FASN (F: TGATCCGGGAGCCGAAGCCA, R: GCCACTGGGCCTCGGGGATA)

SCD1 (F: CCGGACACGGTCACCCGTTG, R: CGCCTTGCACGCTAGCTGGT)

In the incubation phase of the RealTime PCR protocol; UDG is kept at 50ºC for 2 min to activate the enzyme. AmpliTaq Gold was kept at 95ºC for 10 min to activate the UP enzyme. Amplification was conducted in two phases: phase one involved the conversion of DNA from a double-stranded to a single-stranded configuration (denaturation) at 95°C for 15 seconds; and step 2, the quantitative analysis of RT-PCR using beta-actin (ACTB) as endogenous control to normalize the differential expression of tissues.

To determine the change in gene expression levels, Ct values were normalized to housekeeping Ct values. 2^-(ΔΔCt) values were calculated for each gene.[21]

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics 22.0. The Mann-Whitney U test was used for comparing two groups; The Kruskal-Wallis H test was utilized for comparing multiple groups at once due to the non-normal distribution of the variables used in the intergroup comparisons. Conover's Post Hoc Test was employed for multiple comparisons. The Shapiro-Wilk test was used to assess normality, and the Chi-square test was used to compare categorical data. The cut-off

Table 1. Grade 1, Grade 2 and Grade 3 prognostic factors

Prognostic Factors	Grade 1 (n= 17)		Grade 2 (n= 19)		Grade 3 (n= 18)		p
LVI	Pozitive n (%)	Negative n (%)	Pozitive n (%)	Negative n (%)	Pozitive n (%)	Negative n (%)	
	1 (5.59)	16 (94.1)	3 (15.8)	16 (84.2)	8 (44.4)	10 (55.6)	0.016

point for statistical significance was set as p< 0.05 and raw p values were used.

Ethical approval of this study was approved by Mersin University Clinical Research Ethics Committee (January 31, 2024, No: 02/082).

RESULTS

In this study, the patient groups (n=54) were formed from endometrial tissues of patients diagnosed with endometrioid adenocarcinoma and the control groups (n= 36) were formed from endometrial tissues of healthy subjects. The groups' average age was determined to be close to each other. The mean age of the patient group was 53.259±9.441 and the mean age of the control group was 43.722± 4.011.

There was a correlation between the positivity and negativity of lymphovascular invasion (LVI) in Grade 1, Grade 2 and Grade 3 (p= 0.016). The percentages of LVI in Grade 1, Grade 2 and Grade 3 were 5.59%, 15.8% and 44.4%, respectively (Table 1).

In general, when the differences between SCAP, SREBPF1, FASN and SCD gene expression were analyzed, the gene expresion of the patient group were higher than the gene expression of the control group and statistically significant (p< 0.05) (Table 2, Figure 2).

Statistically significant results were also found when we compared the control and patient groups within themselves. When the controls were compared among themselves, a significant difference was found in FASN (p= 0.014) and SCD (p= 0.0001) gene expressions, while no significant difference was found in SREBPF1 (p= 0.694) and SCAP (p= 0.386) gene expression levels (Table 3, Figure 3).

The proliferative phase group (control 2) had higher FASN and SCD gene expression than the secretory phase group (control 1) (Table 3). SCAP and SREBP1 did not significantly vary between the controls (p= 0.386). (Table 3).

Table 2. Comparison of patient and control group

Genes	Median (Min, Max)	Controls (n= 36)	Patient (n= 54)	p
SREBF1	Median	0.001072	3.0756	0.0001
	Min	0.000112	0.002950	
	Max	1	28.740236	
FASN	Median	0.092115	5.500049	0.0001
	Min	0.000058	0.0002878	
	Max	1	59.691121	
SCD	Median	0.0578115895	2.679471738	0.0001
	Min	0.000007898	0.008820034	
	Max	1	20.32241572	
SCAP	Median	0.00372711	1.10645	0.0001
	Min	0.000077	0.0005	
	Max	1.028827	31.461800	

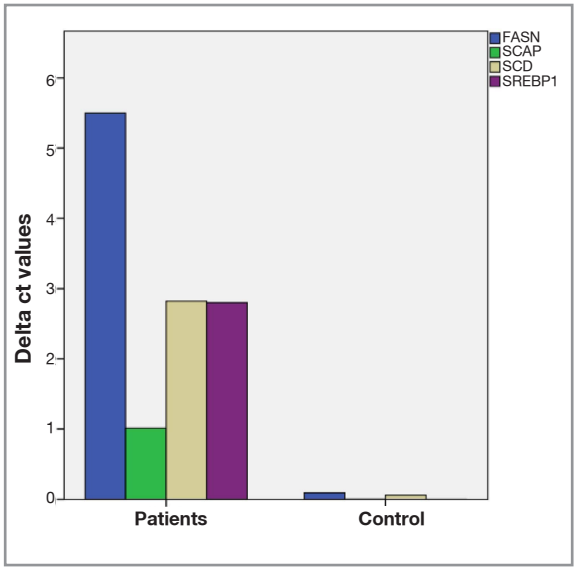

Figure 2. Delta ct values of patient and control.

When the gene expression results of the patient groups were compared, a significant difference was found between the groups only in the SCAP gene (p= 0.005). The SCAP value showed a significant increase in Grade 1 compared to Grade 2, with a post hoc p value of 0.005 (Table 4, Figure 3).

As a result of the Post Hoc test, a difference was found between control 1 and grade 1 (p= 0.0001), grade 2 (p= 0.002), and grade 3 (p= 0.0001) in SCAP, respectively. Similarly, there was a difference between control 2 and grade 1 (p= 0.0001), grade 2 (p= 0.0001), and grade 3 (p= 0.0001), respectively.

DISCUSSION

The increasing prevalence and mortality rates of endometrial cancer (EC) emphasize the necessity for better comprehension and management of this condition.[22,23] Prognostic outcomes are influenced by various factors, including tumor characteristics and metabolic dysregulation.[23,24] This study explores the expression of key regulators of lipid metabolism in EC, such as SCAP, SREBPF1, FASN, and SCD, aiming to reveal their roles in disease mechanisms and identify potential prognostic and therapeutic targets.

Studies have shown that alterations in lipid metabolism, including the expression of key molecules like FASN and SREBPF1, play a crucial role in the energy metabolism of tumor cells, particularly in advanced cancers. Additionally, increased expression of these genes has been associated with cancer cell survival mechanisms and metastasis in various malignancies.[25,26]

Increased FASN expression has been linked to heightened lipid synthesis, which is essential for cell survival mechanisms of cancer cells.[27] Prior

Table 3. Comparison of controls

Genes	Median (Min, Max)	Control 1 (n= 20) (Secretory phase)	Control 2 (n= 16) (Proliferative phase)	p
SREBF1	Median	0.000962	0.001173	0.694
	Min	0.000112	0.000188	
	Max	1	0.225313	
FASN	Median	0.009893	0.105152	0.014
	Min	0.000058	0.027017	
	Max	0.554785	1	
SCD	Median	0.0204038460	0.108986	0.0001
	Min	0.000007898	0.035403	
	Max	0.965936329	1	
SCAP	Median	0.00237083	0.00494864	0.386
	Min	0.000077	0.000502	
	Max	1.028827	0.225313	

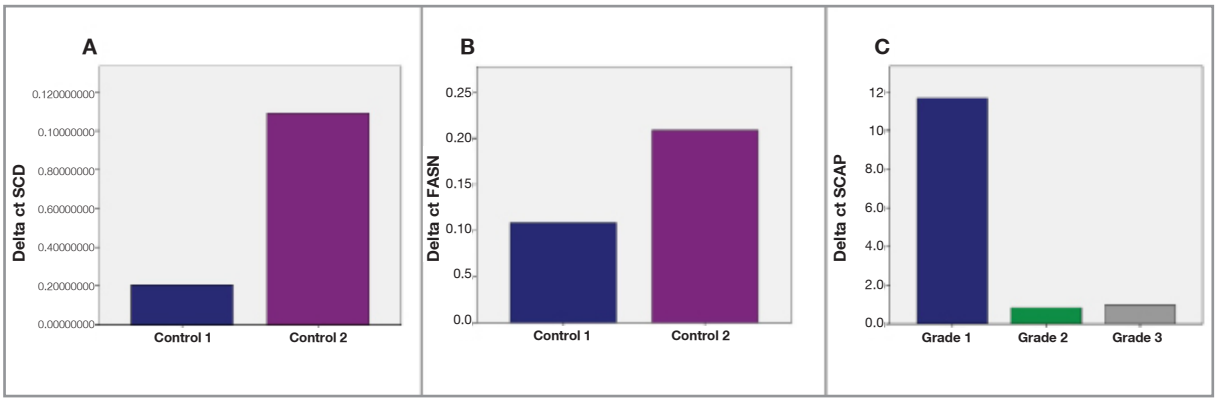

Figure 3. Statistically significant delta ct values in patient and control groups. **A.** Control group SCD delta ct values (Control 1, secretory phase; Control 2, proliferative phase) **B.** Control group FASN delta ct values (Control 1, secretory phase; Control 2, proliferative phase) **C.** Patient group SCAP delta ct values (Control 1, secretory phase; Control 2, proliferative phase)

studies have associated high FASN expression with poor prognosis and lymph node metastasis in cervical cancer.[28] Our findings indicate increased positivity for lymphovascular invasion (LVI) across cancer grades and elevated FASN levels in endometrial cancer tissues compared to controls, suggesting a potential role of FASN in tumor development and metastasis. Further investigations are needed to establish FASN as a novel prognostic factor and potential therapeutic target for endometrial cancer metastases.

Altered lipid metabolism has been associated with the progression and spread of various malignancies, including endometrial cancer. Targeting key enzymes and transcription factors in the lipid metabolism pathway could be a promising therapeutic strategy to combat cancer progression.[29] Research in pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC) have demonstrated the essential role of SCAP in tumor growth, emphasizing the impact of the SREBP pathway on cancer progression.[30,31] Particularly noteworthy is the increased expression of SCAP and SREBPF1, indicating the significance of the SREBP pathway in endometrial cancer progression. This pathway, known to regulate lipid metabolism in different cancers, likely plays a crucial role in the development of endometrial cancer. For instance, this study reveals a marked increase in SCAP expression, especially in Grade 1 tumors, suggesting a vital role in the early stages of the disease. Our investigations show a significant upregulation of SCAP and SREBPF1 in EC patients compared to controls, with distinct patterns across different disease grades.

In our study, contrasting results were obtained compared to previous research regarding SREBPF1 and FASN expressions in endometrial cancer tissues. This suggests that various factors, such as different molecules or the influence of treatments, demographics, and patient conditions, may impact the expression of these genes.[32]

These findings emphasize the intricate nature of lipid metabolism in cancer progression and suggest that FASN and SREBPF1 expressions could be influenced by various factors. Further research is essential to uncover the underlying mechanisms and explore their potential implications for targeted therapeutic approaches in endometrial cancer.

Recent studies have highlighted the significance of Stearoyl-CoA desaturase 1 (SCD1) in various cancers, showcasing its oncogenic role in prostate cancer, papillary thyroid carcinoma, and osteosarcoma.[33,34] Similarly, our findings showed a significant increase in SCD expression in endometrial cancer tissues compared to healthy tissues, aligning with existing literature. However, no notable differences were found in SCD expression levels among different cancer grades, underscoring the need for further investigation to ascertain SCD's potential as a critical biomarker in endometrial cancer.

Table 4. Comparison of Grade 1, Grade 2 ve Grade 3

Genes	Median (Min, Max)	Grade1 (n= 17)	Grade2 (n= 19)	Grade3 (n= 18)	p
SREBF1	Median	2.305373	3.642679	3.520961	0.311
	Min	0.129857	0.319746	0.002950	
	Max	10.374716	28.740236	23.670200	
FASN	Median	7.941681	4.593024	4.788071	0.608
	Min	1.394207	0.687506	0.002878	
	Max	14.117810	59.691121	45.237411	
SCD	Median	2.818641510	2.436820527	4.013887	0.876
	Min	0.439825	0.306721244	0.008820034	
	Max	8.724061861	20.32241572	15.508637070	
SCAP	Median	11.6764	0.855900	0.923700	0.005
	Min	0.068200	0.018700	0.000500	
	Max	31.461800	8.727300	18.070000	

While acknowledging limitations such as sample size constraints and retrospective data analysis, our results provide new insights into the SCAP-SREBP pathway and associated genes in endometrial cancer. Future larger studies, functional analyses and comprehensive assessments of lipid metabolism pathways are necessary to confirm these findings and fully investigate their clinical relevance.

Our study highlighted the significant upregulation of SCAP, SREBPF1, FASN and SCD genes in endometrial cancer tissues, revealing the important role of lipid metabolism in the pathogenesis of this cancer type. The reprogramming of lipid metabolism is integral to meeting the energy demands of tumor cells and targeting these metabolic pathways presents promising therapeutic avenues.

Conclusion

This study underscores the significant role of lipid metabolism reprogramming in the progression of endometrial cancer, with particular focus on the SCAP-SREBP pathway and its associated genes. The observed upregulation of SCAP, SREBPF1, FASN, and SCD genes in cancer tissues suggests that these molecules could serve as potential biomarkers and therapeutic targets. However, while the elevation of FASN and SCD in patients is notable, it remains an observational finding, and it would be more accurate to consider tumor cell dependence on these genes as a possibility rather than a definitive conclusion. This is further supported by the higher expression levels observed during the proliferative phase. Future studies are needed to validate these findings through functional experiments and to explore their translational potential in therapeutic strategies for endometrial cancer.

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