Online ISSN 3007-3197
Print ISSN 3007-3189
DOI 10.5281/zenodo.15906627
http://amresearchreview.com/index.php/Journal/about

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 7 (2025)

Targeting Metabolic Alterations In Endometrial Cancer: Novel Therapeutic Strategies And Mechanisms Of Resistance

[1]Siddiqua Sahar, [2]Kashaf Ali, [3]Hiba Imtiaz, [4]Ariba Nazir, [5]Fiza Sajid, [6]Amna Jarral, [7]Asma Nawaz, [8]Rida Zareen Farooq

Article Details

Keywords: Endometrial Cancer, Metabolic Alterations, Metabolic Interventions, Biomarkers, Chemoresistance

Siddiqua Sahar
Fazaia Ruth Pfau Medical College Karachi, Pakistan
Kashaf Ali
HITEC-IMS Medical College Taxila Cantt, Pakistan
Hiba Imtiaz
Fazaia Ruth Pfau Medical College Karachi, Pakistan
Ariba Nazir
Fazaia Ruth Pfau Medical College Karachi, Pakistan
Fiza Sajid
Fazaia Ruth Pfau Medical College Karachi, Pakistan
Amna Jarral
Fazaia Ruth Pfau Medical College Karachi, Pakistan
Asma Nawaz
Fazaia Ruth Pfau Medical College Karachi, Pakistan
Rida Zareen Farooq
International Medical University, Moscow, Russia

ABSTRACT

The significance and contributory role of metabolic alterations in endometrial cancer cell's pathogenesis, development, and metastasis cannot be overstated. Aerobic glycolysis, the hallmark of cancer cells is found to be complemented by other metabolic alterations such as OXPHOS, hyperglycemia, hyper insulinemia, and dyslipidemia. These metabolic alterations not only serve the role of a potent energy supply, but have some other critical functions such as Epithelial Mesenchyma transition, microenvironment regulation, and therapeutic resistance. The metabolic targeting interventions in the form of experimental and repurposed medications, hormonal drugs, enzyme inhibitors, combination therapies, lifestyle changes, and othershave been showing promising results indicating apotential to offer both augmented as well as individualized treatment options. However, EC cell's inherent capability to adapt to metabolic interventions could pose serious challenges. Several metabolic biomarkers such as AIB1 overexpression, unregulated GLUT1, CSF1/CSF1R, and elevated levels of Nrf2 and GSH were found to be associated with therapeutic resistance and poor prognosis in EC cells. These biomarkers not only provides better diagnostic measures but could also become the novel targets in precision metabolic interventions.

Received on 23 May 2025
Accepted on 22 June 2025
Published on 15 July 2025

INTRODUCTION

Cancer cells have known to undergo numerous metabolic adaptations to maintain a potent energy supply necessary for supporting their rapid growth, invasion, and metastasis. The preferential use of aerobic glycolysis over oxidative phosphorylation (OXPHOS), also known as Warburg effect, is one of the hallmark metabolic adaptations in the cancer cells[i]. However, most recent evidence indicates that glycolysis and oxidative phosphorylation work together to create a metabolic symbiosis between cancer cells and its micro-environment, maximizing the energy potential for tumor growth and progression[ii]. Other metabolic changes in a cancer cell include up-regulated lipid metabolism, increased amino acid metabolisms, and altered metabolic interactions with the microenvironment. This metabolic reprogramming not only supplies the requisite energy for growth, invasion, and metastasis, but also have been found to play a critical role in enhancing cancer cells resistance against chemotherapy, radiotherapy, and targeted interventions by affecting events like redox, homeostasis, apoptosis, and autophagy. Therefore, advancements in understanding the link between these metabolic adaptations and cancer could pave the way for novel therapeutic strategies and provide auxiliary treatments which could improve chemotherapy outcomes

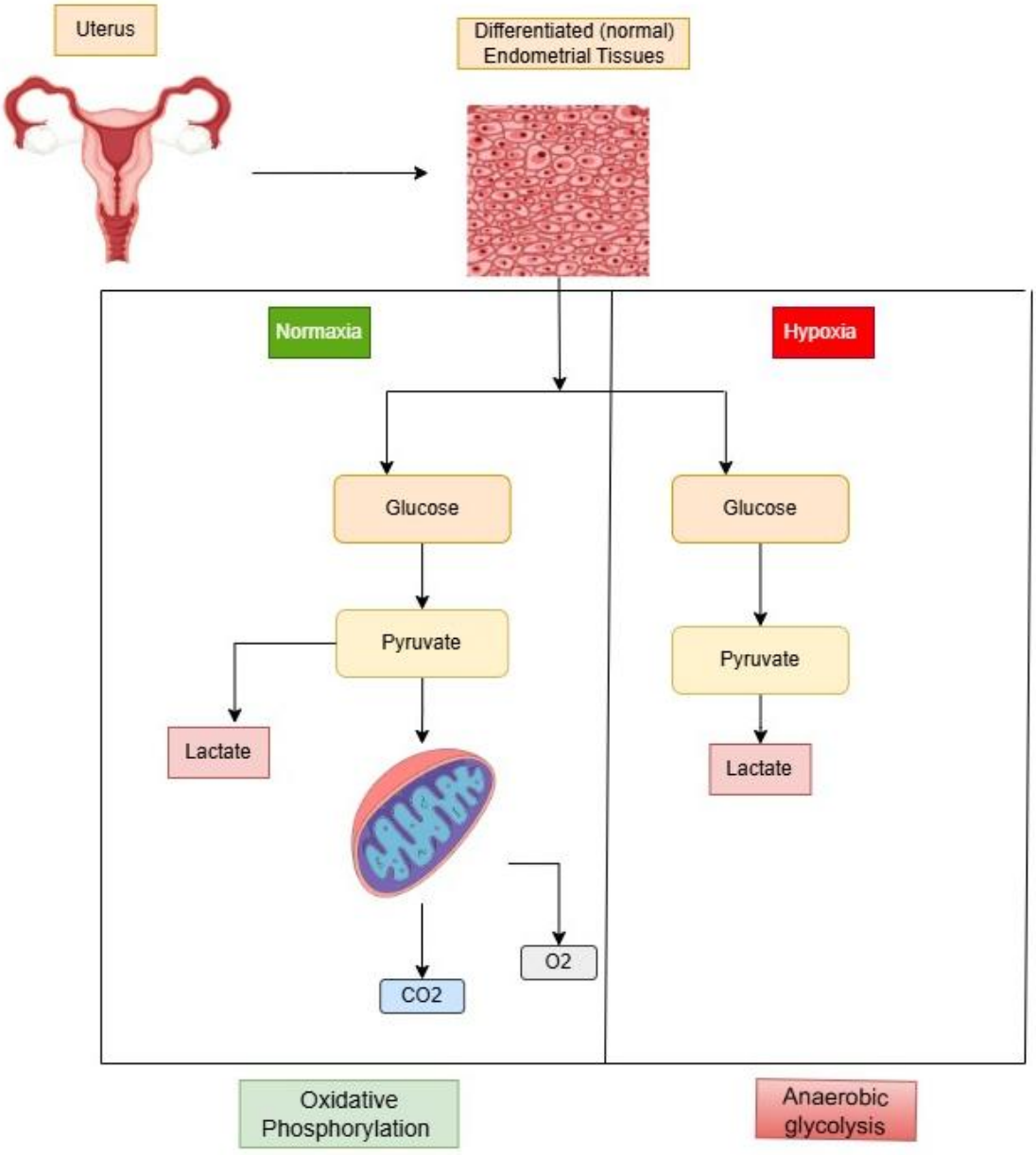


FIGURE 1: OXPHOS AND GLYCOLYSIS IN NORMAL ENDOMETRIAL CELLS

Endometrial cancer has become one of the most prevalent gynecologic malignancies, particularly in high-income countries. 417,367 new cases of corpus uteri or endometrial cancer were reported in 2020 which accounts for 2.2% of all reported cancer cases in 2020. Moreover, 97,370 women lost their life to EC, accounting for 1% of the all cancer related deaths in 2020[iii]. In contrast to the declining or plateaued incidence and mortality rates of other solid tumor, the trajectory of endometrial cancer's incidence and mortality rates have increased in the past three decades. According to Global Burden of Disease (2017), Endometrial Cancer (EC) had an age standardized

incidence and mortality rate of 0.58% and 0.89% respectively[iv]. Of note, the highest incidence rates were observed in developed regions like North America and Western Europe[v]. This increase in the incidence and mortality rates of EC is ascribed to increased incidence rates of metabolic syndromes which are most closely linked to the pathogenesis, development, and prognosis of EC as compared to other gynecologic malignancies.

Empirical evidence from epidemiological studies suggest that among gynecologic cancers, EC is most closely linked to the Metabolic Syndromes (MetS). The incidence and development of EC is often associated with metabolic syndrome particularly, hyperglycemia, hypertension, dyslipidemia, and obesity. Moreover, obesity, diabetes, and hypertension (the EC triad) are prevalent in women following the onset of EC. A clinical research revealed that diabetic patients were 2.12 more likely to develop EC than a normal person and overweight women with BMI greater than 25 kg/m2 were 2.45 times more likely to develop EC. Moreover, overweight women with hypertension issues were at 3.5 times higher risk to develop EC than a normal woman. Similarly, the results of a prospective control study revealed that women with recent diagnosis of EC cancer had a higher incidence rate of hyperglycemia, cardiovascular risk factors, and HDL cholesterol ratio. Thus, a close link between endometrial cancer and metabolic syndrome is self-evidentiary. However, the mechanism through which MetS influence the incidence rates and progression of EC has not been fully explored. Also, the causal link between metabolic syndromes (MetS) and metabolic reprogramming is yet to be established. Regardless, the close relationship of MetS and metabolic reprogramming with endometrial cancer cannot be ignored as practitioners and scientists around the globe have started to treat EC as a metabolic disorder instead of merely being a hormone-dependent tumor.

Prolonged overstimulation of endometrium caused by extended exposure to elevated estrogen in the absence or limited supply of progesterone antagonism has traditionally been considered the primary driver of endometrial cancer. According to this pathogenesis model, unopposed estrogen either binds with estrogen receptors (ERs) in nucleus, taking over the control of specific target genes transcription or triggers a non-genomic estrogen signaling mechanism via Ca^{2+} influx which leads to non-genomic cancer proliferation[1]. Based on these

[1]Estrogen binds with G protein-coupled estrogen receptor (GPER) leading to Ca^{2+} influx via cell membrane. The influx of Ca^{2+}, in turn, stimulate downstream signaling via MAPK/Erk pathway, promoting non-genomic cancer proliferation.

models, long-term progesterone therapy has been commonly used as a clinical treatment for EC despite its normal effective rate (50-70%) and high recurrence chances (40%). Contrary to the wide held belief, recent studies suggest that serum estrogen levels in EC were comparable to the estrogen levels in the control group. Similarly, the prolonged estrogen exposure in post-menopausal women were found to pose no additional risk of endometrial cancer. In addition, the traditional model of EC pathogenesis do not explain the onset of EC in post-menopausal women with insignificant estrogen levels in their bloodstream. Thus, the evidence suggests that contrary to the previously held beliefs, long term exposure to elevated estrogen levels may not be the primary cause of the onset and proliferation of EC. Instead, other factors like local sensitivity to estrogen and metabolic alterations may play a critical role in EC onset and progression[vi].

This review article provides a comprehensive overview of the literature on metabolic reprogramming in the endometrial cancer cells and their microenvironment, aiming to offer a robust understanding of its role in the cancer progression and resistance against existing therapies. Moreover, the article also explores the novel metabolic-targeting interventions, evaluating their effectiveness and molecular mechanisms observed thus far in experimental (*in vitro* and *in vivo*) and clinical research. In the end, the article aims to identify any potential metabolic biomarkers associated with therapeutic resistance and prognosis.

METABOLIC ALTERATIONS IN ENDOMETRIAL CANCER CELLS

Metabolic reprogramming plays a crucial role in controlling key aspects of cancer cell functions by either directly or indirectly influencing pathogenesis, growth, or metastasis. The primary metabolic alterations in EC cells include increased glycolytic activity and reduced oxidative phosphorylation.

INCREASED GLYCOLYTIC ACTIVITY (WARBURG EFFECT)

Increased glycolytic activity is the hallmark of endometrial cancer cells generally demonstrated by increased glycolytic enzymes in the cell lines of endometrial cancer patients. Empirical evidence from various in-vivo and in-vitro studies indicate that in contrast to normal individuals, glycolytic enzymes and transporters such as HK2, GLUT6, LDHA, and PKM2 are overexpressed in EC cell lines. For instance, overexpression of Hydrokinase (HK2) enzyme was observed in EC tissues, promoting Epithelial-to-mesenchymal transition (EMT) and aerobic glycolysis by activating Focal Adhesion Kinase (FAK) and its downstream signaling pathway (ERK1/2)[vii]. These experimental findings have been triangulated using clinical evidence. Consistent with the results of experimental findings, a higher concentration of glycolytic

enzymes and transporters such as PKM2, GLUT, LDH, and ENO1 was observed in EC cells as compared to normal endometrial cells[viii].

Interestingly, recent studies indicate a heterogeneity in glycolytic activity and enzymes based on histological variant of EC (Type I or Type II). Cell lines of EC type II (HEC-1, KLE, and AN3CA), an aggressive version of EC with low survival rate, exhibited relatively lower glycolytic activity. Of note, KLE cell line showed the least glycolytic, fatty acid, and OXPHOS metabolism despite the elevated levels of glycolytic enzymes. These cell lines usually rely on glutamine oxidation for fulfilling their energy needs. In contrast, some cell lines like MFE-319 and RL95–2 have up-regulated glycolytic activity but low levels of glycolytic enzymes, mainly PKM2[ix]. Therefore, EC cell lines are generally marked by increased glycolysis. However, the levels of glycolytic enzymes may vary based on cell line type. Similarly, EC cells were found to exhibit metabolic heterogeneity with three distinct subtypes categorised on the basis of metabolic pathways. These three metabolism-pathway-based subtypes (MPS1, MPS2, and MPS3) showed distinct characteristics such as different stages of metabolic activity, genomic alterations, and response to immunotherapy.[x] Therefore, the heterogeneity of the EC cell lines and histology must be considered before developing and implementing metabolism targeted therapeutic interventions.

Metabolic syndromes like diabetes, high BMI index, and increased cholesterol levels result in chronic inflammation. Prolonged inflammation causes accumulation of harmful molecules like reactive oxygen species (ROS) and changes in oncogenic signaling pathways (AMPK/mTOR/S6, TGF-β, JAK/STAT, MAPK, Wnt/β)[xi]. These alterations in molecular mechanisms along with elevated-estrogen-driven mutations in mitochondrial RNA (in the absence of progesterone antagonism) induce metabolic reprogramming in tumor cells, favoring glycolysis and tumor growth. Moreover, Insulin-like Growth Factor Binding Protein 2, IGFBP2 has been found to contribute in cell proliferation and glycolysis by controlling enzymes like pyruvate kinase M2 and hypoxia-inducible factor 1-alpha dimer, (PKM2/ HIF-1α)[xii]. The elevated levels of insulin and glucose levels, common in diabetes type 2, influence the levels of IGFBP2 in bloodstream. Thus, metabolic syndromes may have a contributory role in metabolic reprogramming in EC, promoting glycolysis and inhibiting OXPHOS.

In addition to fueling key oncogenic processes such as tumor growth, proliferation, and metastasis, glycolysis plays a crucial role in regulating microenvironment and developing chemotherapy resistance. Lactate, a byproduct of glycolysis is produced inside the EC cell and

then transported outside through lactate transporters like MCT1 and MCT4. The higher concentration of lactate results in acidic tumor microenvironment, which in turn plays crucial role in angiogenesis and immunosuppression. Moreover, Lactate has been found to perform several other functions like acting as a fuel for neighboring cells (Lactate Shuttle), inducing Epithelial-Mesenchymal transition, and triggering downstream signaling through GPR81[xiii]. Thus, targeting lactate through inhibitors or transporters is emerging as a potential therapeutic surgery for EC patients. However, this treatment may suppress endometrial receptivity because high concentration of lactate and thereof acidic medium potentially plays a crucial role in mediating the maternal-fetal dialogue, improving the chances of natural and assisted pregnancies[xiv]. Similarly, increased glycolytic activity is known to induce therapeutic resistance by helping cancer cells evade apoptosis, changing metabolic pathways, and influencing interstitial pressure[xvxvixviixviii].

The extant literature on metabolic alterations in endometrial cancer accentuates the importance of heightened glycolysis in EC cells' growth, metastasis, and therapeutic resistance. In addition to acting as an instant energy source for EC cell's rapid anabolic activities, the lactate produced as a byproduct promote angiogenesis and immunosuppression by regulating the cell's microenvironment. Moreover, the heightened glycolytic activity is believed to be associated with EC cell's resistance against general therapies. The link between metabolic syndromes and increased glycolytic activity and heterogeneity of EC cell's metabolic activity based on EC cell lines are some important avenues that could significantly contribute to the understanding of metabolic alterations.

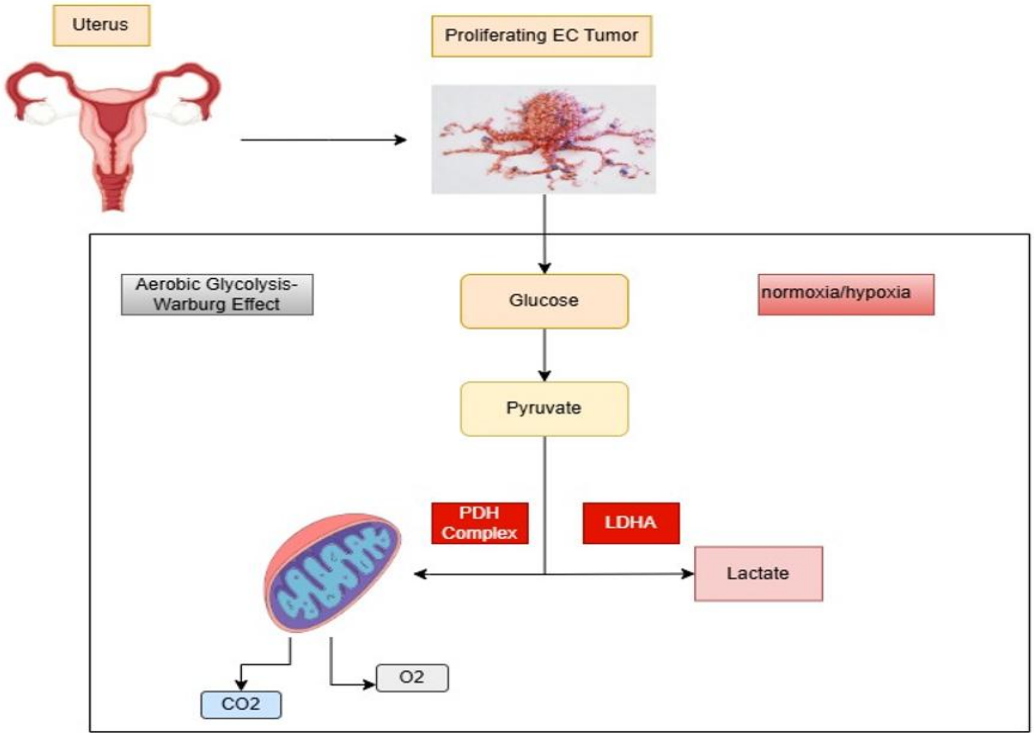


FIGURE 2: ANAEROBIC AND AEROBIC GLYCOLYSIS IN ENDOMETRIAL CANCER CELLS

OXPHOS AND METABOLIC PLASTICITY

It is generally believed that oxidative phosphorylation (OXPHOS), which is a preferential energy source in differentiated normal cells, in the presence of oxygen, becomes impaired or suppressed in endometrial cancer cells. Cancer cells turn to glycolysis (Warburg effect) for energy generation which is otherwise an emergency energy source for hypoxic conditions. This shift in the cancer cells is known to be induced by genetic mutation in mitochondrial DNA. 69% of the EC cells in an in-Vitro study were found to have mutated mitochondrial DNA, suggesting a potential to become a significant EC biomarker. These mutations are known to influence electron transport chain, particularly the Complex I which results in faulty mitochondria respiration and reduced OXPHOS efficiency[xix]. The hypoxic microenvironment also plays a crucial role in influencing the shift from OXPHOS to Glycolysis by the action of hypoxia-inducible factor 1-alpha dimer (HIF-1α)[xx].

Even though endometrial cancer studies have mostly focused on glycolysis and availability of literature on OXPHOS and its molecular mechanism in EC cells is limited, the evidence from other gynecologic malignancies indicate that cells transition between OXPHOS

and glycolysis based on unique changes in the cancer cell's microenvironment and other factors. Thus, in light of the recent evidence, OXPHOS activity is not fully suppressed in gynecologic malignancies. Rather, cancer cells create a metabolic symbiosis, effectively utilsing all available resources needed for the metabolic activities involved in cancer cell's rapid division, proliferation, and metastasis. Some studies even suggest that some malignancies like high OXPHOS subtype melanoma, pancreatic ductal adenocarcinoma, and lymphomas may have up-regulated OXPHOS activity even in the face of glycolysis[xxi]. Moreover, some cancer cells are known to acquire a hybrid phenotype developing their ability to transition between glycolysis and OXPHOS, known as metabolic plasticity. This hybrid phenotype is observed in some cancer stem cells and chemo-resistant EC cells, notably in Cisplatin.

The results of in-vitro study indicates that a mitochondria targeted antioxidant, Mito6-TPP induced cytotoxic activity in cancer cells by modulating intracellular ROS (Reactive Oxygen Species) levels and inducing apoptosis, showing selectivity for cancerous cells[xxii]. Hence, drawing on the recent body of evidence, mitochondria has emerged as a potential target for metabolic interventions targeting metabolic plasticity of cancer cells. Moreover, more research is needed on OXPHOS suppression and its link with EC development and prognosis.

HYPERGLYCEMIA AND HYPERINSULINEMIA

Hyperglycemia has always been known to enhance the risks of endometrial cancer. However, previously, the link between diabetes mellitus and EC were controversial. A meta-analysis based study have made the breakthrough, suggesting a direct link between diabetes and the EC risk by controlling other factors like BMI[xxiii] and race[xxiv]. More recent studies have found hyperglycemia to be an independent risk factor for EC, particularly associated with poor prognosis in EC type I[xxv]. Strategies like bariatric surgeries and glucose-lowering drugs are known to reduce the risk of EC, particularly, in patients with metabolic syndromes like obesity and diabetes. Moreover, prolonged exposure to elevated glucose levels in the bloodstream is known to impair cellular respiration and induce insulin resistance or hyperinsulinemia, creating a vicious positive feedback cycle.

Hyperinsulinemia often correlated with obesity, non-insulin dependent diabetes mellitus, and polycystic ovary syndrome is found to enhance the risk of endometrial cancer. Recent evidence suggests that a pancreatic insulin marker, C-peptide, enhanced the EC cancer risk with an odds ratio of 4.76 for the highest quintile. Similarly, decreased levels of IGF binding factor protein IGBF-1 and 2 are also found to multiply the chances of EC cancer by deregulating

insulin like growth factors. Role of hyperinsulinemia in therapeutic resistance is also known because elevated insulin is known to influence MEK/ERK pathway, supporting their survival and proliferation[xxvi]. The metabolic alterations related to hyperinsulinemia and its role in promoting EC are summarized in Table 1. Similarly, metformin, an anti-diabetic drug has been known to give promising results for EC patients. Thus, hyperglycemia and in turn hyperinsulinemia are two important metabolic changes that promotes the progression and therapeutic resistance in EC patients.

DYSLIPIDEMIA

Emerging evidence indicate a strong correlation between abnormal lipid metabolism and the development and progression of EC. The elevated levels of enzymes and transcription factors such as Fatty Acid Synthase (FASN) Sterol Regulatory Element-Binding Protein 1 (SREBP1), Stearoyl-CoA Desaturase 1 (SCD1) and other has been reported in EC patients (Table 1). The atypical high levels of triglycerides, building blocks of lipids, have been observed in EC patients. A study targeting Swedish AMORIS cohort, found that women in the fourth quartile of triglycerides level had the hazard ratio of 1.57 as compared to the women in the first quartile. Similarly, a high concentration of low-density lipoprotein cholesterol and a low concentration of high-density cholesterol (HDL-C) were found to be associated with higher EC risk[xxvii]. Another cohort based study revealed that the EC patients were found to have high triglyceride and glycated hemoglobin compared to those with endometrial hyperplasia, suggesting the viability of triglycerides to glucose ratio as an emerging biomarker for EC progression and prognosis[xxviii]. Mechanistically, the role of dyslipidemia in influencing EC can be attributed to several pathways. For instance, high triglycerides level is known to regulate estrogen by binding to sex hormone binding globulin (SHGB). Similarly, disrupted lipid metabolism can produce increased level of free radicals that cause inflammation, promoting carcinogenesis. Moreover, dyslipidemia is also associated with EMT, thus promoting EC cell's metastasis. Consistent with the metabolic link of dyslipidemia with EC, cholesterol lowering statin has been found to improve the survival rate of EC patients, particularly in EC type II. Therefore, targeting lipid metabolism can also be a novel therapeutic approach in EC patients and several preclinical trials have already begun (Table 2).

TABLE 1: METABOLIC ALTERATIONS IN ENDOMETRIAL CANCER

Metabolic Pathway	Enzyme / Molecule	Alteration in EC	Role / Impact in EC	Evidence Type	Ref
Glycolysis	HK2	↑	Promotes glycolysis; supports proliferation	In vitro, Clinical	[xxix]
	PFKFB3	↑	Enhances glycolytic flux and resistance	In vitro, Clinical	[30]
	LDHA	↑	Facilitates lactate production; aggressive phenotype	Clinical	[xxx]
	PKM2	↑	Maintains Warburg metabolism	In vitro	[xxxi]
	GLUT6	↑	Increases glucose uptake	Clinical	[xxxii]
OXPHOS	ATP Synthase (Complex V)	↑	Linked to increased tumor growth and poor prognosis	In vitro, Clinical	[xxxiii]
	COX Subunits	↑	Enhances OXPHOS efficiency; supports progression	In vitro, In vivo	[xxxiv]
	Mitochondrial Complexes	Variable	Reprogramming contributes to chemoresistance	Review	[21]
Hyperinsulinemia / Glucose Uptake	Insulin Receptor (IR)	↑	Promotes proliferation and survival	In vitro, Clinical	[26]
	IRS-1	↑	Activates downstream PI3K/AKT pathway	In vitro, Clinical	[37]
	PI3K	↑	Enhances glucose uptake and cell growth	In vitro, Clinical	[xxxv]
	AKT	↑	Promotes metabolic	In vitro,	[37]

			reprogramming	Clinical	
	mTOR	↑	Enhances growth and metabolic activity	In vitro, Clinical	[38]
	GLUT4	↑	Increases glucose uptake	In vitro, Clinical	[xxxvi]
	P-LAP/IRAP	↑	Facilitates GLUT4 translocation	In vitro, Clinical	[xxxvii]
Lipid Metabolism	FASN	↑	Drives lipogenesis; poor prognosis	In vitro, Clinical	[xxxviii] [xxxix]
	ACC1	↑	Enhances fatty acid synthesis	In vitro	[41]
	SREBP1	↑	Activates lipogenic genes	In vitro, Clinical	[xl]
	SCD1	↑	Supports membrane fluidity and aggressiveness	In vitro	[43]
	CPT1A	↓	Reduced fatty acid oxidation	In vitro	[xli]
	ACLY	↑	Links glucose to lipid synthesis	In vitro, Clinical	[26]
	ACSL4	↑	Activates fatty acids for biosynthesis	In vitro	[41]
	FABP4	↑	Enhances lipid transport and tumor growth	In vitro, Clinical	[41]
Amino Acid Metabolism	GLS	↑	Supports glutamine utilization and biosynthesis	In vitro, Clinical	[xlii]
	ASCT2 (SLC1A5)	↑	Facilitates glutamine uptake	In vitro, Clinical	[46]
	PHGDH	↑	Drives serine biosynthesis;	In vitro,	[xliii]

		poor prognosis	Clinical	
IDO1	↑	Depletes tryptophan; promotes immune evasion	In vitro, Clinical	[xliv]
LAT1 (SLC7A5)	↑	Imports essential amino acids; drives growth	In vitro, Clinical	[48]

METABOLIC INTERVENTIONS

Numerous studies indicate that experimental drugs targeting metabolic changes in EC have shown prominence in inhibiting tumor growth and apoptosis. 2-Deoxyglucose (2-DG) has been found to have a metabolic antagonistic action with Hexokinase (HK) in glycolysis, altering metabolite profiles ultimately leading to glycolysis inhibition[xlv]. Similarly, CB-839 (Telaglenastat) inhibits Glutaminase (GLS) in glutamine metabolism reducing proliferation and glutamine metabolism, while also promoting autophagy[xlvi]. Another study found that FX11 inhibits Lactate Dehydrogenase-A (LDHA) leading to reduced glycolytic activity and enhanced reactive oxygen species (ROS) production, resulting in tumor suppression[xlvii]. Moreover, Pyruvate Dehydrogenase Kinase (PDK) has been targeted by Dichloroacetates (DCA), shifting metabolism to oxidative phosphorylation (OXPHOS) resulting in decreased proliferation and apoptosis induction[xlviii]. A G6PD inhibitor, Polydatin, was linked with disrupting Pentose Phosphate Pathway (PPP) of glucose metabolism, increasing the production of reactive oxygen species (ROS) thus inhibiting cancer cell survival[xlix]. The compound Azaphenothiazine derivative (compound 33) was also found to decrease tumor growth by acting upon GRP75 proteins, impairing calcium homeostasis within mitochondria leading to decreased tumor growth[l].

Repurposed medications that target underlying metabolic changes in EC has also shown potential in both clinical and preclinical research. Metformin has anticancer effects as it activates AMPK pathway and inhibits mTOR which suppresses both in vitro and clinical tumors[li]. Mitochondrial Complex I also gets inhibited, reducing the stem-like EC cell lactate survival[lii]. It was also observed that EC patients experienced increased metabolic and proliferative resistance to EC after treatment with Metformin during the clinical trial[liii]. EC cell proliferation and invasion were suppressed by Buformin which activates AMPK and Inhibits mTOR[liv]. FASN inhibitor Orlistat has also shown positive results in EC patients by interfering with fat metabolism which decreases the growth rate and increases the rate of apoptosis[lv]. Disulfiram from ALDH inhibition increases cell ROS and reduces cell viability having synergistic effects when mixed with radiation[lvi]. Lastly, Simvastatin also has shown positive results on EC tumor

suppression by suppressing HMG-CoA which increases the rate of cholesterol metabolism and reduces the proliferation of EC cells[lvii].

Hormonal therapies based on the metabolic pathways in EC are currently in clinical and preclinical investigations. STX64, or irosustat, an inhibitor of steroid sulfatase STS, substantially controlled circulating estrogens and tumor-promoting signaling during advanced EC phase II clinical trials[lviii]. Aromatase inhibitors, such as letrozole, were found to be effective in hormone-sensitive EC patients due to their capability to lower estradiol production[lix]. Additionally, Medroxyprogesterone acetate (MPA) serves as a progesterone receptor pathway inhibitor and suppresses proliferation through PI3K/AKT/mTOR glycolytic and lipidomic cell metabolism. Fulvestrant is also reported to downregulate estrogen receptors (ER) and thus decrease expression of ERα and proliferation in positive hormone EC cells[lx]. SERM tamoxifen has a limited application for EC as it tends to induce some hyperplasia while in other cases, restricting growth[lxi].

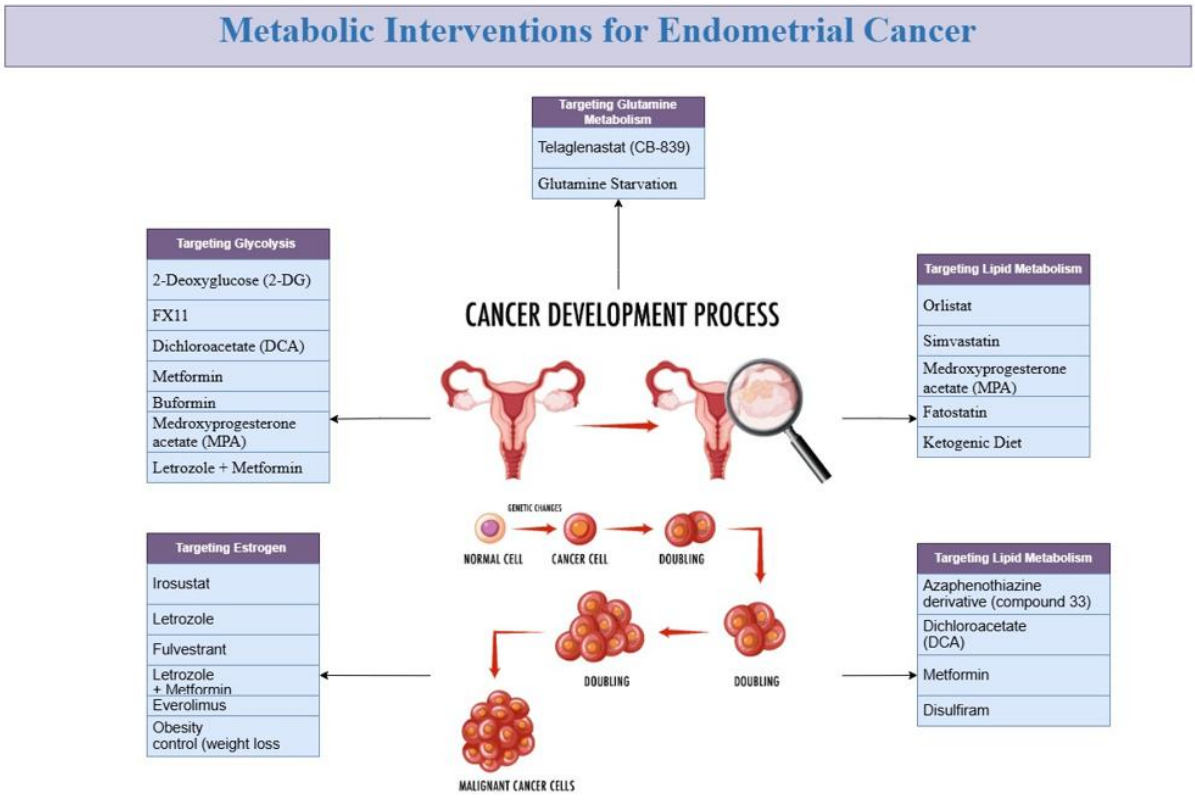
The role of enzyme inhibitors in targeting metabolic changes in EC cells are also being investigated. CB-839 (Telaglenastat), an inhibitor of Glutaminase (GLS), has been found to reduce glutamine metabolism, slowing tumor growth and progression[48]. Orlistat, a FASN (Fatty Acid Synthase) inhibitor, induce lipogenetic apoptosis in EC cells[55]. Fatostatin, an SREBP1 inhibitor, reduces fatty acid synthesis and reverses progesterone resistance[51]. A G6PD polydatin inhibitor disrupts the Pentose Phosphate Pathway (PPP) causing an increase in ROS and increased apoptosis[lxii].

Additionally, clinical trials have also demonstrated some therapeutic options for endometrial cancer (EC) associated with metabolic syndromes. In the Phase II trial, Metformin use uncovered an anticancer effect (reduced tumor proliferation and mTOR signaling) in obese EC patients[52]. The Irosustat Phase II trial demonstrated reduced estrogen-driven tumor signaling, but patients did not experience any added benefit compared to megestrol acetate[58]. Letrozole and Metformin are currently being studied in a Phase II trial, demonstrating anti-proliferative synergy in hormone-sensitive EC tumors[lxiii]. Another study also supported the use of simvastatin in reducing EC risk [57].

Combination therapies aimed at the metabolic pathways in endometrial cancer (EC) are particularly effective. Metformin and Letrozole increase the activity of AMPK, mTOR and Aromatase, yielding strong antiproliferative clinical results[lxiv]. Metformin + Progestin (MPA) EC cell lines regain sensitivity to progestin and exhibit diminished proliferation and glycolysis[lxv].

Everolimus + Letrozole achieves stabilization in advanced/recurrent EC[63]. Simvastatin, with radiation, leads to increased radiosensitivity and oxidative stress [64]. Disulfiram + radiation enhances reactive oxygen species (ROS), significantly improving the outcomes as compared to radiotherapy alone[56].

Lastly, dietary changes, nutrient restriction methods, and lifestyle habits are essential for modifying the metabolism of endometrial cancer (EC). Glutamine starvation targets glutamine metabolism and has been shown to reduce proliferation, increase autophagy, and induce metabolic collapse in EC cells[lxvi]. Caloric restriction (CR) improves cancerous EC growth in mice by acting through IGF-1, mTOR, and AMPK; this enhances apoptosis/senescence and slows down proliferation [44]. A ketogenic diet (KD) also decreases the rate of tumor progression by depriving tumors of glucose and promoting the use of fatty acids for oxidation[lxvii]. Metformin combined with CR has shown greater anti-tumor activity compared to Metformin or CR alone, suggesting a synergy for more excellent treatment capability[52]. Obesity control and aerobic exercise have improved EC prognosis and associated lower recurrence rates for the disease, thus, linked with better prognosis and lower EC risk[lxviii].



Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 7 (2025)

TABLE 2: METABOLIC INTERVENTIONS FOR ENDOMETRIAL CANCER

Intervention Type	Pathway Targeted	Therapeutic Strategy	Molecular Target	Model Type	Observed Effects	Study Stage	Reference
Experimental Drug	Glycolysis	2-Deoxyglucose (2-DG)	Hexokinase (HK)	In vitro	Altered metabolite profiles, inhibited glycolysis	Preclinical	[45]
	Glutamine metabolism	CB-839 (Telaglenastat)	Glutaminase (GLS)	In vitro, In vivo	↓ proliferation, ↓ glutamine metabolism, ↑ autophagy	Preclinical	[46]
	Glycolysis	FX11	LDHA (Lactate Dehydrogenase A)	In vitro, In vivo	↓ tumor growth, ↑ ROS, ↓ glycolysis	Preclinical	[47]
	Glycolysis / OXPHOS balance	Dichloroacetate (DCA)	Pyruvate Dehydrogenase Kinase (PDK)	In vitro	↓ proliferation, ↑ apoptosis, metabolic shift to OXPHOS	Preclinical	[48]
	Pentose Phosphate Pathway (PPP)	Polydatin	G6PD (Glucose-6-Phosphate Dehydrogenase)	In vitro, In vivo	↓ proliferation, ↑ apoptosis, ↑ ROS		[49]
	Mitochondrial	Azaphenothiazine	GRP75	In vitro, In	↓ proliferation, ↓	Preclinical	[50]

	calcium homeostasis	derivative (compound 33)		vivo	migration, ↑ apoptosis, ↓ tumor growth		
Repurposed Drug	Glycolysis, mTOR	Metformin	AMPK activation, mTOR inhibition	In vitro, Clinical	↓ mTOR signaling, ↓ proliferation, ↓ tumor growth	Preclinical & Phase II Trial	[51[53]]
	Mitochondrial bioenergetics	Metformin	Mitochondrial Complex I	In vitro	↓ mitochondrial membrane potential, ↑ lactate, ↓ EC stem-like cell survival	Preclinical	[52]
	Glycolysis, mTOR	Buformin	AMPK activation, mTOR inhibition	In vitro	↓ proliferation, ↓ invasion, anti-metabolic effects	Preclinical	[54]
	Lipid metabolism	Orlistat	Fatty Acid Synthase (FASN)	In vitro	↓ FASN activity, ↓ proliferation, ↑ apoptosis	Preclinical	[55]
	Redox metabolism,	Disulfiram	ALDH	In vitro	↑ ROS, ↓ cell	Preclinical	[56]

	glutathione detox		inhibition		viability, synergistic effect with radiation		
	Cholesterol / lipid metabolism	Simvastatin	HMG-CoA reductase	In vitro	↓ cholesterol synthesis, ↓ EC cell proliferation	Preclinical	[57]
Hormonal Agent	Estrogen metabolism	Irosustat (STX64 / BN83495)	Steroid sulfatase (STS)	Clinical	↓ circulating estrogens, reduced tumor-promoting signaling	Phase II Clinical Trial	[58]
	Estrogen biosynthesis	Letrozole	Aromatase (CYP19A1)	In vitro, Clinical	↓ estradiol production, effective in hormone-sensitive EC	Clinical Use in Hormone Receptor+ EC	[59]
	Glycolysis, lipid metabolism (via PI3K/AKT/mTOR)	Medroxyprogesterone acetate (MPA)	Progesterone receptor pathway	In vitro, Clinical	↓ glycolysis, ↓ lipid synthesis, ↓ proliferation	Clinical	[65]
	Estrogen signaling	Fulvestrant	Estrogen receptor downregulation	In vitro	↓ ERα expression, ↓ proliferation in hormone receptor-positive EC cells	Preclinical	[60]

	Estrogen signaling	Tamoxifen	Estrogen receptor modulator (SERM)	In vitro, Clinical	Mixed effects: can induce hyperplasia but may reduce growth in select cases	Limited EC-specific use	[61]
Nutrient-Deprivation	Glutamine metabolism	Glutamine starvation	Glutamine uptake (ASCT2 / SLC1A5)	In vitro	↓ proliferation, ↑ autophagy, metabolic collapse	Preclinical	[67]
Enzyme Inhibitor	Glutamine metabolism	CB-839 (Telaglenastat)	Glutaminase (GLS)	In vitro, In vivo	↓ glutamine use, ↓ tumor growth	Preclinical	[48]
	Lipid metabolism	Orlistat	Fatty Acid Synthase (FASN)	In vitro	↓ lipogenesis, ↑ apoptosis	Preclinical	[55]
	Lipid metabolism	Fatostatin	SREBP1 (lipogenesis regulator)	In vitro	↓ fatty acid synthesis, reversed progesterone resistance	Preclinical	[51]
	Pentose Phosphate Pathway (PPP)	Polydatin	Glucose-6-phosphate dehydrogenase (G6PD)	In vitro, In vivo	↑ ROS, ↓ cell survival, ↓ PPP activity		[62]
Clinical Trial	Glycolysis, mTOR	Metformin	AMPK	Clinical Trial	↓ tumor	Phase II	[52]

		activation, mTOR inhibition	(Phase II)	proliferation markers (Ki-67), ↓ mTOR signaling in obese EC patients		
Estrogen metabolism	Irosustat (STX64)	Steroid sulfatase (STS)	Clinical Trial	Reduced estrogen-driven tumor signaling; no significant superiority over megestrol acetate	Phase II	[58]
Estrogen & Glycolysis	Letrozole + Metformin	Aromatase & AMPK/mTOR	Clinical Trial (Ongoing)	Combination showing anti-proliferative synergy in hormone-sensitive EC	Phase II (ongoing)	[63]
Lipid metabolism	Simvastatin	HMG-CoA reductase	Clinical (Retrospective study)	Suggested reduced EC risk and slower progression in statin users	Observational / Retrospective	[57]
Glycolysis / mTOR / Hormone	Everolimus + Letrozole	mTOR pathway + Estrogen	Clinical Trial	Stabilized disease in advanced/recurrent		[lxix]

					EC; metabolic modulation suggested		
Combination Therapy	AMPK, mTOR, Aromatase	Metformin	Letrozole	Glycolysis + Estrogen	Clinical	↓ Ki-67, potential synergistic antiproliferative effect	[64]
	AMPK, mTOR + PR	Metformin	Progestin (MPA)	Glycolysis + Hormone signaling	In vitro, Clinical	Resensitized EC cells to progestin; ↓ proliferation, ↓ glycolysis	[70]
	mTOR + Estrogen receptor	Everolimus	Letrozole	mTOR, Hormonal signaling	Clinical	Disease stabilization in advanced/recurrent EC	[63]
	HMG-CoA reductase	Simvastatin	Radiation	Lipid + ROS metabolism	In vitro	↑ Radiosensitivity, ↑ oxidative stress, ↓ viability	[64]
	ALDH inhibition	Disulfiram	Radiation	Redox metabolism	In vitro	↑ ROS, synergistic EC cell killing with radiation	[56]
Dietary	Glycolysis, mTOR	Caloric Restriction	IGF-1 / mTOR	↓ tumor	In vivo (mouse EC	Preclinical	[44]

Intervention		(CR)	/ AMPK modulation	growth, ↓ proliferation, ↑ apoptosis	model)		
	Glycolysis, Lipid metabolism	Ketogenic Diet (KD)	Glucose deprivation / ↑ fatty acid oxidation	↓ Glucose availability, ↑ ketone utilization, reduced tumor progression	In vivo (mouse EC model)	Preclinical	[68]
Dietary + Drug	Glycolysis + Hormonal	Metformin + CR	AMPK / mTOR	Enhanced anti-tumor effects vs. metformin or CR alone	In vivo	Preclinical	[52]
Lifestyle Factor	Glycolysis, Estrogen signaling	Obesity control (weight loss)	Insulin resistance / estrogen production	↓ EC risk, improved prognosis, lower recurrence rates	Clinical (cohort studies)	Observational	[lxx]
	Glycolysis, mTOR	Exercise (aerobic)	AMPK /	↑ Insulin	Clinical (pilot	Pilot Clinical	[69]

Insulin sensitivity	levels, potential anti-tumor metabolic effects	studies)	Studies

THERAPEUTIC RESISTANCE

The role of metabolic alterations in therapeutic resistance in EC cells cannot be overstated. For instance, metabolic plasticity (flexibility of cells to shift between Aerobic glycolysis and OXPHOS for energy supply), has emerged as a major contributor to drug resistance in metabolism oriented interventions. For instance, therapies targeting 2-DG, Metformin, DCA, showed therapeutic resistance most likely attributed to the metabolic plasticity. Similarly, another study reveals the improved role of metmorfins in inhibiting cancer cell proliferation, via inhibiting glycolysis. However, due to cancer cells have known to adapt to these intervention via striking a balance between shift to glycolysis, fatty acid oxidation (FAO) and OXPHOS[lxxi]. Similarly, hyperglycemia induced elevated levels of pyruvate dehydrogenase kinase 1 (PDK1) having a role in metformin resistance, dyslipidemia induced resistance mechanism driven by FASN and SREBP1 and many others metabolic adaptations have been discovered in metabolic targeted interventions (Table 3).

Similarly,cancer cells adopt to metabolic therapies by developing alternative pathways of metabolism. For instance, FASN inhibition by Orlistat compel cancer cells to adapt by other pathways of lipid synthesis (desaturases, elongases) and increased expression of CD36, fatty acid transport proteins, to enhance uptake of fatty acids from blood.Moreover, cancer cells may also activate redundant pathways. For instance, up regulation of acetyl-CoA carboxylase, which partially compensates for loss of FASN activity. Therefore, the prospect of lipid metabolism targeting therapeutic interventions does not look promising, unless a cohort intervention targeting multiple pathways at once is institutionalized.

The review of novel metabolic resistances in recent targeted interventions has uncovered several biomarkers of therapeutic resistance. For instance, mutations in PIK3CA and PTEN, AIB1 overexpression, unregulated GLUT1, immune-metabolic markers like CSF1/CSF1R, and antioxidant defenses like elevated levels of Nrf2 and GSH could be treated as biomarkers of therapeutic resistance. These biomarkers are known to represent metabolic alterations in EC cells, having a significant role in therapeutic evasion. Thus, they not only correlates with therapeutic resistance mechanisms, but could also offer measurable targets in diagnostics and precision therapy.

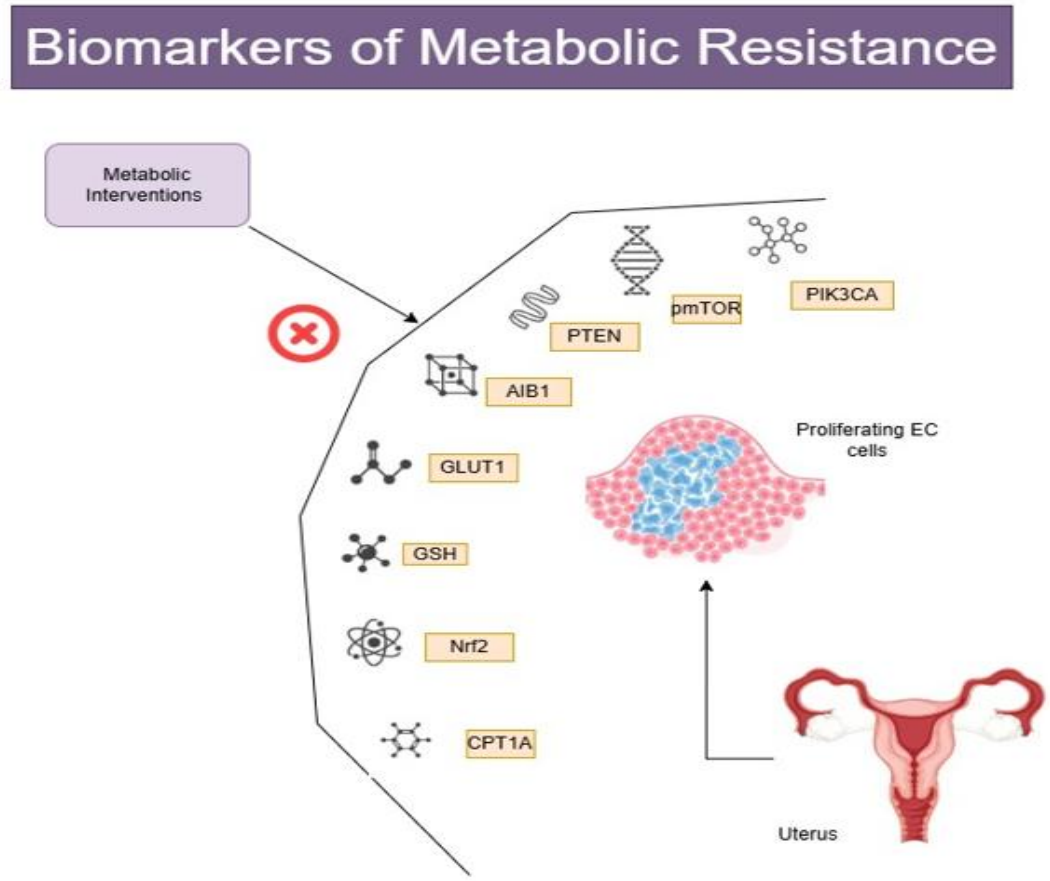


FIGURE 4: BIOMARKERS OF METABOLIC RESISTANCE IN EC CELLS

TABLE 3: NOVEL METABOLIC RESISTANCES AND BIOMARKERS

Resistance Mechanism	Targeted Therapy	Adaptation and potential Biomarkers	Outcome	Model	Reference
Metabolic plasticity	2-DG, Metformin, DCA	Glycolysis → OXPHOS/FAO shift	Reduced drug sensitivity	In vitro, In vivo	[70]
Redundant pathways	Orlistat (FASN)	Increased lipid uptake, FAO	Compensates for FASN block	In vitro	[69]
PI3K/PTEN/mTOR mutation	Everolimus	PIK3CA mutation, PTEN loss	Persistent mTOR activity	Clinical, In vitro	[lxxii]
Hormone receptor loss	Progestins, Letrozole	Decreased PR/ER expression	Hormone resistance	In vitro, Clinical	[lxxiii]
Epigenetic reprogramming	SREBP1 inhibitors, hormones	Histone/chromatin changes	Increased metabolic gene expression	In vitro	[lxxiv]
Tumor microenvironment	IDO1, Glutamine starvation	Hypoxia, immune evasion	Drug escape	Preclinical, 3D models	[lxxv]
Antioxidant response	Disulfiram, FX11	Increased GSH, Nrf2, detox enzymes	Reduced ROS-mediated killing	In vitro	[lxxvi]
Elevated Glycolysis	Paclitaxel	Increased GLUT1 production mediated via TMPO-AS1/miR-140/143	Chemotherapy resistance	In vitro	[15]
Insulin Feedback loop/alternative pathways activation	Temsirolimus -P13/AKT inhibitor	PTEN mutation pmTOR	PR=14% SD=69% Vs PR=4%	Phase II Clinical Trials	[lxxvii]

			SD=48%		
Warburg effect	Targeting AIB1-coactivator	AIB1 overexpression mediated glycolysis. Acetylation by PCAF, and AIB1 binding to c-myc.	Tomor growth and poor prognosis	Homozygous mice cell endometrial line (In vivo)	[lxxviii]
Metabolic reprogrammming via MAPK	Nano-particles (Selumetinib)	CSF1, CSF1R	Macrophage transition from M2 to M1 and MAPK signaling induced tumor suppression	In-vivo	[lxxix]

CONCLUSION

This article aimed to analyze the mechanistic role of metabolic alterations in Endometrial Cancer, uncovering novel metabolic interventions, and therapeutic resistance biomarkers. The review of the extant literature in this domain revealed several valuable insights that can have both practical and theoretical implications. First, the review of studies on metabolic alterations revealed that Warburg effect, hyperglycemia, hyperinsulinemia, and dyslipidemia were among the major metabolic alterations. Among these the role of OXPHOS in EC cell metabolism is found to be an under-researched area. Contrary to the generally held belief that OXPHOS is impaired in EC cells, recent evidence indicate a symbiotic relationship between OXPHOS and glycolysis, regulated by the EC cells' microenvironment. Thus, the role of OXPHOS warrants more research as mitochondria can become a novel metabolic target in EC cells. Moreover, the heterogeneity of the EC cells based on cell line and histology are also important avenue of research as they demonstrate different glycolytic activity, prognosis, and response to therapeutic interventions. Moreover, the link of dyslipidemia and hyperglycemia induced insulin resistance were also found to have significant association with EC tumor growth, development, and metastasis.

Secondly, a comprehensive review of the metabolic intervention was conducted. The results

suggest that using experimental and repurposed medications, treating endometrial cancer (EC) with hormones, enzyme inhibitors, combination therapies, lifestyle changes, and other metabolic-focused measures have the potential for better outcomes. These measures could not only augment the therapeutic strategies to improve the survival of the EC patients, but also improve the individualized treatment options, leading to reduced recurrence, and therefore, long-term improved prognosis for EC patients.

The final aim of this review article was to identify metabolic biomarkers associated with therapeutic resistance and poor prognosis. A better understanding of these novel resistance mechanisms associated with metabolic alterations presents a great opportunity to unravel novel biomarkers and therapeutic targets, supporting improved prognosis and cancer treatment. Review of the literature on metabolic intervention in EC cells revealed several novel metabolic resistance mechanisms associated with inducing therapeutic resistance in EC cells. These biomarkers are known to represent metabolic alterations in EC cells, having a significant role in therapeutic evasion. Thus, they not only correlates with therapeutic resistance mechanisms, but could also offer measurable targets in diagnostics and precision therapy.

REFERENCES

[i]Li, J., Yang, H., Zhang, L., Zhang, S. and Dai, Y., 2023. Metabolic reprogramming and interventions in endometrial carcinoma. *Biomedicine & Pharmacotherapy*, *161*, p.114526.

[ii]Martínez-Reyes I, Chandel NS. Cancer metabolism: looking forward. Nature Reviews Cancer. 2021 Oct; 21(10):669-80.

[iii]Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021 May; 71(3):209-49.

[iv]Zhang, S., Gong, T.T., Liu, F.H., Jiang, Y.T., Sun, H., Ma, X.X., Zhao, Y.H. and Wu, Q.J., 2019. Global, regional, and national burden of endometrial cancer, 1990–2017: results from the global burden of disease study, 2017. *Frontiers in oncology*, *9*, p.1440.

[v]Feng J, Lin R, Li H, Wang J, He H. Global and regional trends in the incidence and mortality burden of endometrial cancer, 1990–2019: updated results from the Global Burden of Disease Study, 2019. Chinese Medical Journal. 2024 Feb 5; 137(03):294-302.

[vi]Yang X, Wang J. The role of metabolic syndrome in endometrial cancer: a review. Frontiers in oncology. 2019 Aug 8; 9:744.

[vii]Dong P, Xiong Y, Konno Y, Ihira K, Kobayashi N, Yue J, Watari H. Long non-coding RNA DLEU2 drives EMT and glycolysis in endometrial cancer through HK2 by competitively binding with miR-455 and by modulating the EZH2/miR-181a pathway. Journal of Experimental & Clinical Cancer Research. 2021 Jun 26; 40(1):216.

[viii]Li J, Yang H, Zhang L, Zhang S, Dai Y. Metabolic reprogramming and interventions in endometrial carcinoma. Biomedicine & Pharmacotherapy. 2023 May 1; 161:114526.

[ix]Aune D, Sen A, Vatten LJ. Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies. Scientific reports. 2017 Apr 7; 7(1):44808.

[x]Liu X, Wang W, Zhang X, Liang J, Feng D, Li Y, Xue M, Ling B. Metabolism pathway-based subtyping in endometrial cancer: An integrated study by multi-omics analysis and machine learning algorithms. Molecular Therapy-Nucleic Acids. 2024 Jun 11; 35(2).

[xi]Han J, Zhang L, Guo H, Wysham WZ, Roque DR, Willson AK, Sheng X, Zhou C, Bae-Jump VL. Glucose promotes cell proliferation, glucose uptake and invasion in endometrial cancer cells via AMPK/mTOR/S6 and MAPK signaling. Gynecologic oncology. 2015 Sep 1; 138(3):668-75.

[xii]Jin Y, Qi M, Si L, Shi X, Cai M, Fu H, Liu Y, Guo R. IGFBP2 Promotes Proliferation and Glycolysis of Endometrial Cancer by Regulating PKM2/HIF-1α Axis. Cancer Science.

[xiii]Pérez-Tomás R, Pérez-Guillén I. Lactate in the tumor microenvironment: an essential molecule in cancer progression and treatment. Cancers. 2020 Nov 3; 12(11):3244.

[xiv]Gurner KH, Evans J, Hutchison JC, Harvey AJ, Gardner DK. A microenvironment of high lactate and low pH created by the blastocyst promotes endometrial receptivity and implantation. Reproductive BioMedicine Online. 2022 Jan 1; 44(1):14-26.

[xv]Dong P, Wang F, Taheri M, Xiong Y, Ihira K, Kobayashi N, Konno Y, Yue J, Watari H. Long non-coding RNA TMPO-AS1 promotes GLUT1-mediated glycolysis and paclitaxel resistance in endometrial cancer cells by interacting with miR-140 and miR-143. Frontiers in Oncology. 2022 May 27; 12:912935.

[xvi]Tian S, Ren L, Liu C, Wang Z. Atractylenolide II suppresses glycolysis and induces apoptosis by blocking the padi3-erk signaling pathway in endometrial cancer cells. Molecules. 2024 Feb 21; 29(5):939.

[xvii]Mori Y, Yamawaki K, Ishiguro T, Yoshihara K, Ueda H, Sato A, Ohata H, Yoshida Y, Minamino T, Okamoto K, Enomoto T. ALDH-dependent glycolytic activation mediates

stemness and paclitaxel resistance in patient-derived spheroid models of uterine endometrial cancer. Stem cell reports. 2019 Oct 8; 13(4):730-46.

[xviii]Han X, Sheng X, Jones HM, Jackson AL, Kilgore J, Stine JE, Schointuch MN, Zhou C, Bae-Jump VL. Evaluation of the anti-tumor effects of lactate dehydrogenase inhibitor galloflavin in endometrial cancer cells. Journal of hematology & oncology. 2015 Dec; 8:1-4.

[xix]Cormio A, Cormio G, Musicco C, Sardanelli AM, Gasparre G, Gadaleta MN. Mitochondrial changes in endometrial carcinoma: Possible role in tumor diagnosis and prognosis. Oncology reports. 2015 Mar; 33(3):1011-8.

[xx]Smolarz B, Łukasiewicz H, Samulak D, Kołaciński R, Langner S, MAKOWSKA M, ROMANOWICZ H. Hypoxia-induced Factor-1α and its Role in Endometrial Cancer. Anticancer Research. 2024 Sep 1;44(9):3697-712.

[xxi]Ashton TM, McKenna WG, Kunz-Schughart LA, Higgins GS. Oxidative phosphorylation as an emerging target in cancer therapy. Clinical Cancer Research. 2018 Jun 1; 24(11):2482-90.

[xxii]Castelôa M, Moreira-Pinto B, Benfeito S, Borges F, Fonseca BM, Rebelo I. In vitro effects of mitochondria-targeted antioxidants in a small-cell carcinoma of the ovary of hypercalcemic type and in type 1 and type 2 endometrial cancer. Biomedicines. 2022 Mar 29; 10(4):800.

[xxiii]Saed L, Varse F, Baradaran HR, Moradi Y, Khateri S, Friberg E, Khazaei Z, Gharahjeh S, Tehrani S, Sioofy-Khojine AB, Najmi Z. The effect of diabetes on the risk of endometrial Cancer: an updated a systematic review and meta-analysis. BMC cancer. 2019 Dec; 19:1-0.

[xxiv] Wartko PD, Beck TL, Reed SD, Mueller BA, Hawes SE. Association of endometrial hyperplasia and cancer with a history of gestational diabetes. Cancer Causes & Control. 2017 Aug; 28:819-28.

[xxv]Wang Y, Liu Q, Sun Y, Wu W, Cheng X, Chen X, Ren F. Association between metabolic disorders and clinicopathologic features in endometrial cancer. Frontiers in Endocrinology. 2024 Aug 26; 15:1351982.

[xxvi]Wang Y, Zhu Y, Zhang L, Tian W, Hua S, Zhao J, Zhang H, Xue F. Insulin promotes proliferation, survival, and invasion in endometrial carcinoma by activating the MEK/ERK pathway. Cancer letters. 2012 Sep 28; 322(2):223-31.

[xxvii]Seth D, Garmo H, Wigertz A, Holmberg L, Hammar N, Jungner I, Lambe M, Walldius G, Van Hemelrijck M. Lipid profiles and the risk of endometrial cancer in the Swedish AMORIS study. International journal of molecular epidemiology and genetics. 2012 May 15; 3(2):122.

[xxviii]Wang X, Li Y, Hou X, Li J, Ma X. Lipid metabolism reprogramming in endometrial cancer: biological functions and therapeutic implications. Cell Communication and Signaling. 2024 Sep 10; 22(1):436.

[xxix]Xiao Y, Jin L, Deng C, Guan Y, Kalogera E, Ray U, Thirusangu P, Staub J, Sarkar Bhattacharya S, Xu H, Fang X. Inhibition of PFKFB3 induces cell death and synergistically enhances chemosensitivity in endometrial cancer. Oncogene. 2021 Feb 25; 40(8):1409-24.

[xxx]Giatromanolaki A, Sivridis E, Gatter KC, Turley H, Harris AL, Koukourakis MI. Lactate dehydrogenase 5 (LDH-5) expression in endometrial cancer relates to the activated VEGF/VEGFR2 (KDR) pathway and prognosis. Gynecologic oncology. 2006 Dec 1; 103(3):912-8.

[xxxi]Yang W, Xia Y, Hawke D, Li X, Liang J, Xing D, Aldape K, Hunter T, Yung WA, Lu Z. PKM2 phosphorylates histone H3 and promotes gene transcription and tumorigenesis. Cell. 2012 Aug 17; 150(4):685-96.

[xxxii] Byrne FL, Poon IK, Modesitt SC, Tomsig JL, Chow JD, Healy ME, Baker WD, Atkins KA, Lancaster JM, Marchion DC, Moley KH, Ravichandran KS, Slack-Davis JK, Hoehn KL. Metabolic vulnerabilities in endometrial cancer. Cancer Res. 2014 Oct 15; 74(20):5832–45.

[xxxiii]Liu M, Xu Y, Zhou Y, Lang R, Shi Z, Zhao J, Meng Y, Bao L. Integrated analyses reveal the multi-omics and prognostic characteristics of ATP5B in breast cancer. Frontiers in genetics. 2021 May 28; 12:652474.

[xxxiv] Ikeda K, Horie-Inoue K, Suzuki T, et al. Mitochondrial supercomplex assembly promotes breast and endometrial tumorigenesis by metabolic alterations and enhanced hypoxia tolerance. Nat Commun. 2019; 10:4108.

[xxxv] Kyo S, Nakayama K. Endometrial cancer as a metabolic disease with dysregulated PI3K signaling: Shedding light on novel therapeutic strategies. Int J Mol Sci. 2020; 21(17):6073.

[xxxvi] Zhang X, Lu JJ, Abudukeyoumu A, Hou DY, Dong J, Wu JN, Liu LB, Li MQ, Xie F. Glucose transporters: Important regulators of endometrial cancer therapy sensitivity. Front Oncol. 2022; 12:933827.

[xxxvii] Shibata K, Kajiyama H, Ino K, et al. P-LAP/IRAP-induced cell proliferation and glucose uptake in endometrial carcinoma cells via insulin receptor signaling. BMC Cancer. 2007; 7:15.

[xxxviii] Mokhtari K, Pérez-Jiménez A, García-Salguero L, Lupiáñez JA, Rufino-Palomares EE. Unveiling the differential antioxidant activity of maslinic acid in murine melanoma cells and in

rat embryonic healthy cells following treatment with hydrogen peroxide. Molecules. 2020; 25(17):4020.

[xxxix] Rai P, Lokesh CR, Goel A, Aggarwal R. Endoscopic ultrasound-guided choledochoduodenostomy using partially-covered self-expandable metal stent in patients with malignant distal biliary obstruction and unsuccessful ERCP. Endosc Int Open. 2018; 6(1):E67–E72.

[xl] Wei R, Penso NEC, Hackman RM, Wang Y, Mackenzie GG. Epigallocatechin-3-gallate (EGCG) suppresses pancreatic cancer cell growth, invasion, and migration partly through the inhibition of Akt pathway and epithelial-mesenchymal transition: Enhanced efficacy when combined with gemcitabine. Nutrients. 2019; 11(8):1856.

[xli] Farahzadi R, Hejazi MS, Molavi O, Pishgahzadeh E, Montazersaheb S, Jafari S. Clinical significance of carnitine in the treatment of cancer: From traffic to the regulation. Oxid Med Cell Longev. 2023; 2023:9328344.

[xlii] Guo J, Fan J, Zhang Y, Li M, Jin Z, Shang Y, Zhang H, Kong Y. Progesterone inhibits endometrial cancer growth by inhibiting glutamine metabolism through ASCT2. Biosci Rep. 2024; 44(3):BSR20232035.

[xliii] Zhang H, Kong W, Zhao X, et al. Comprehensive analysis of PHGDH for predicting prognosis and immunotherapy response in patients with endometrial carcinoma. BMC Med Genomics. 2023; 16:29.

[xliv] Li C, Chen S, Jia W, Li W, Wei D, Cao S, Qian Y, Guan R, Liu H, Lei D. Identify metabolism-related genes IDO1, ALDH2, NCOA2, SLC7A5, SLC3A2, LDHB, and HPRT1 as potential prognostic markers and correlate with immune infiltrates in head and neck squamous cell carcinoma. Front Immunol. 2022; 13:955614.

[xlv] Urakami K, Zangiacomi V, Yamaguchi K, Kusuhara M. Impact of 2-deoxy-D-glucose on the target metabolome profile of a human endometrial cancer cell line. Biomed Res. 2013; 34(5):221-9.

[xlvi] Zhou WJ, Zhang J, Yang HL, Wu K, Xie F, Wu JN, Wang Y, Yao L, Zhuang Y, Xiang JD, Zhang AJ, He YY, Li MQ. Estrogen inhibits autophagy and promotes growth of endometrial cancer by promoting glutamine metabolism. Cell Commun Signal. 2019; 17(1):99.

[xlvii] Han JH, Lee E, Park W, Ha K, Chung H. Natural compounds as lactate dehydrogenase inhibitors: Potential therapeutics for lactate dehydrogenase inhibitors-related diseases. Front Pharmacol. 2023; 14:1275000.

[xlviii] Wong JY, Huggins GS, Debidda M, Munshi NC, De Vivo I. Dichloroacetate induces apoptosis in endometrial cancer cells. Gynecol Oncol. 2008; 109(3):394–402.

[xlix] Mele L, Paino F, Papaccio F, Regad T, Gambardella G, Ghannad-Rezaie M, et al. A new inhibitor of glucose-6-phosphate dehydrogenase blocks pentose phosphate pathway and suppresses malignant proliferation and metastasis in vivo. Cell Death Dis. 2018; 9:572.

[l] Mao F, Kong D, Wang H, et al. Discovery of Novel Azaphenothiazine Derivatives to Suppress Endometrial Cancer by Targeting GRP75 to Impair Its Interaction with IP3R and Mitochondrial Ca^{2+} Homeostasis. *J Med Chem.* 2024; 67(16):11823-11836.

[li] Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation—implications for a novel treatment strategy. Gynecol Oncol. 2010; 116(1):92–8.

[lii] Kraus D, Rechberger V, Fritsch H, et al. The Diminishment of Novel Endometrial Carcinoma-Derived Stem-like Cells by Targeting Mitochondrial Bioenergetics and MYC. *Int J Mol Sci.* 2022;23(5):2426.

[liii] Schuler KM, Rambally BS, DiFurio MJ, Sampey BP, Gehrig PA, Makowski L, Bae-Jump VL. Antiproliferative and metabolic effects of metformin in a preoperative window clinical trial for endometrial cancer. Cancer Med. 2015; 4(2):161–73.

[liv] Zubiria I, Garcia-Rodriguez A, Atxaerandio R, Ruiz R, Benhissi H, Mandaluniz N, et al. Effect of feeding cold-pressed sunflower cake on ruminal fermentation, lipid metabolism and bacterial community in dairy cows. Animals (Basel). 2019;9(10):755.

[lv] Wysham WZ, Roque DR, Han J, Zhang L, Guo H, Gehrig PA, et al. Effects of fatty acid synthase inhibition by orlistat on proliferation of endometrial cancer cell lines. Target Oncol. 2016; 11(6):763–9.

[lvi] Waller DA, Hazeltine E, Wessel JR. Common neural processes during action-stopping and infrequent stimulus detection: The frontocentral P3 as an index of generic motor inhibition. Int J Psychophysiol. 2021; 163:11–21.

[lvii] Chen ZJ, Yang XL, Liu H, Wei W, Zhang KS, Huang HB, et al. Bisphenol A modulates colorectal cancer protein profile and promotes the metastasis via induction of epithelial to mesenchymal transitions. Arch Toxicol. 2015; 89(8):1371–81.

[lviii] Cancer Research UK. A trial looking at irosustat to treat advanced womb cancer [Internet]. London: Cancer Research UK; [cited 2025 Apr 6]. Available at:

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-irosustat-treat-advanced-womb-cancer

[lix] Hu X, Hu Y, Li G. Development of novel molecularly imprinted solid-phase microextraction fiber and its application for the determination of triazines in complicated samples coupled with high-performance liquid chromatography. J Chromatogr A. 2007; 1147(1):1–9.

[lx] de Vries EG, Gietema JA, de Jong S. Tumor necrosis factor-related apoptosis-inducing ligand pathway and its therapeutic implications. Clin Cancer Res. 2006; 12(8):2390–3.

[lxi] Geier M, Bosch OJ, Boeckh J. Ammonia as an attractive component of host odour for the yellow fever mosquito, Aedes aegypti. Chem Senses. 1999; 24(6):647–53.

[lxii] Song S, Choi K, Ryu SW, Kang SW, Choi C. TRAIL promotes caspase-dependent pro-inflammatory responses via PKCδ activation by vascular smooth muscle cells. *Cell Death Dis.* 2011; 2 (11):e223.

[lxiii] ClinicalTrials.gov. Metformin in Treating Patients With Endometrial Cancer [Internet]. Bethesda (MD): National Library of Medicine (US); 2007– [updated 2022 Jan 10; cited 2025 Apr 6]. Report No.: NCT02065687. Available at: https://clinicaltrials.gov/study/NCT02065687

[lxiv] Rietveld T, Vegter RJK, van der Slikke RMA, Hoekstra AE, van der Woude LHV, de Groot S. Wheelchair mobility performance of elite wheelchair tennis players during four field tests: inter-trial reliability and construct validity. *PLoS One.* 2019; 14(6):e0217514.

[lxv] Hsieh PF, Chueh PJ, Liu PF, Liao JW, Hsieh MK. Immune response evoked by tumor-associated NADH oxidase (tNOX) confers potential inhibitory effect on lung carcinoma in a mouse model. Am J Cancer Res. 2019; 9(4):740–51.

[lxvi] Zhao Q, Lin X, Wang G. Targeting SREBP-1-mediated lipogenesis as potential strategies for cancer. Front Oncol. 2022;12:952371.

[lxvii] McKeigue PM, Spiliopoulou A, McGurnaghan S, Colombo M, Blackbourn L, McDonald TJ, et al. Persistent C-peptide secretion in type 1 diabetes and its relationship to the genetic architecture of diabetes. *BMC Med.* 2019; 17(1):165.

[lxviii] O'Neill HM. AMPK and exercise: glucose uptake and insulin sensitivity. *Diabetes Metab J.* 2013; 37(1):1–21.

[lxix] Chang JJ, Sanossian N. Pre-hospital glyceryl trinitrate: potential for use in intracerebral hemorrhage. *J Neurol Disord.* 2013; 2(1):141.

[lxx] Guntur SR, Choi MJ. An improved tissue-mimicking polyacrylamide hydrogel phantom for

visualizing thermal lesions with high-intensity focused ultrasound. *Ultrasound Med Biol.* 2014; 40(11):2680–91.

[lxxi]Zou J, Hong L, Luo C, Li Z, Zhu Y, Huang T, Zhang Y, Yuan H, Hu Y, Wen T, Zhuang W. Metformin inhibits estrogen-dependent endometrial cancer cell growth by activating the AMPK–FOXO 1 signal pathway. Cancer science. 2016 Dec; 107(12):1806-17.

[lxxii] Yang X, Cheng Y, Zhou J, Zhao C, Zhang X, Zhang Q, et al. Targeting cancer metabolism plasticity with JX06 nanoparticles via inhibiting PDK1 combined with metformin for endometrial cancer patients with diabetes. *Adv Sci (Weinh).* 2022; 9(8):e2104472.

[lxxiii] Kurban S, Mehmetoğlu İ. Effects of fatty acid synthase inhibition by orlistat on proliferation of endometrial cancer cell lines. *Eur J Gynaecol Oncol.* 2016; 37(2):265–8.

[lxxiv] Slomovitz BM, Lu KH, Johnston T, Coleman RL, Munsell MF, Broaddus RR, et al. A phase 2 study of the mTOR inhibitor everolimus in patients with recurrent endometrial carcinoma. *Cancer.* 2010; 116(23):5415–9.

[lxxv] Arnett-Mansfield RL, deFazio A, Wain GV, Jaworski RC, Byth K, Mote PA, et al. Relative expression of progesterone receptors A and B in endometrioid cancers of the endometrium. *Cancer Res.* 2001; 61(11):4576–82.

[lxxvi] Yang Y, Liu H, Li Z, Zhao Z, Wang Y, Liu L, et al. The roles and mechanisms of SREBP1 in cancer development and treatment. *Signal Transduct Target Ther.* 2023;8(1):152.

[lxxvii]Oza AM, Elit L, Tsao MS, Kamel-Reid S, Biagi J, Provencher DM, Gotlieb WH, Hoskins PJ, Ghatage P, Tonkin KS, Mackay HJ. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. Journal of Clinical Oncology. 2011 Aug 20; 29(24):3278-85.

[lxxviii]Wu D, Li M, Wang M, Yan Z, Meng Y. PCAF acetylates AIB1 to form a transcriptional coactivator complex to promote glycolysis in endometrial cancer. Frontiers in Oncology. 2024 Sep 5; 14:1442965.

[lxxix]Ramesh A, Brouillard A, Kumar S, Nandi D, Kulkarni A. Dual inhibition of CSF1R and MAPK pathways using supramolecular nanoparticles enhances macrophage immunotherapy. Biomaterials. 2020 Jan 1; 227:119559.