Subtype-specific mechanisms of lipid metabolism in gynecological malignancies and novel targeted intervention strategies (Review)

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Abstract. Dysregulated lipid metabolism, a core metabolic hallmark of gynecological malignancies, plays a pivotal role in the initiation, progression, therapeutic resistance and prognosis of ovarian cancer, endometrial cancer and cervical cancer. Distinct pathological and molecular subtypes of ovarian, endometrial and cervical cancer exhibit highly heterogeneous and subtype-specific lipid metabolic reprogramming patterns, with core phenotypes ranging from enhanced fatty acid oxidation in high-grade serous ovarian cancer to sterol regulatory element-binding protein 1-driven lipogenesis in obesity-associated endometrial cancer and human papillomavirus-mediated cholesterol dysregulation in cervical cancer. These subtype-specific metabolic alterations drive tumor progression by mediating key malignant phenotypes, with mitochondrial lipid metabolism playing a central regulatory role in therapeutic resistance. The present review systematically summarizes the subtype-specific features of lipid metabolic dysregulation in gynecological malignancies, elaborates on the underlying molecular regulatory mechanisms, and summarizes the latest progress in lipid metabolism-targeted intervention strategies and their clinical translation. Finally, the current challenges and future directions in this field are discussed, aiming to provide new insights and theoretical support for the precision treatment of gynecological malignancies.

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1. Introduction

Gynecological malignancies represent a major threat to health, with ovarian, endometrial cancer and cervical cancer ranking among the most prevalent and lethal neoplasms of the female reproductive tract (1-3). Statistics indicate that >1.3 million new cases of gynecological malignancies and nearly 500,000 associated deaths are reported globally each year. Ovarian cancer, in particular, is characterized by insidious onset and challenges in early diagnosis, with >70% of patients presenting at an advanced stage (International Federation of Gynecology and Obstetrics stage III/IV) at the time of diagnosis (4,5). While primary debulking surgery combined with platinum-based chemotherapy can achieve initial remission, the postoperative recurrence rate of ovarian cancer is >70%, with a 5-year survival rate of only ~30%. Platinum resistance stands as the primary bottleneck contributing to treatment failure (6,7). Endometrial cancer has witnessed a steady rise in incidence, with obesity-associated type I endometrial cancer (Bokhman classification) accounting for >80% of cases and conferring a poor prognosis (8). For advanced or recurrent endometrial cancer, therapeutic options remain limited, as immune checkpoint inhibitors only benefit a subset of patients with mismatch repair-deficient subtypes (9). Although early intervention for cervical cancer is feasible through human papillomavirus (HPV) vaccination and screening, high-risk subtypes associated with persistent HPV infection (such as HPV16/18) still pose a risk of disease progression (10-12). Chemoradiotherapy resistance and lymph node metastasis remain critical factors limiting patient outcomes. Collectively, the interplay between subtype heterogeneity, therapeutic resistance and metabolic dysregulation constitutes the core impediment to favorable clinical outcomes in gynecological malignancies (13,14).

Metabolic reprogramming, a hallmark of malignant tumors, is closely linked to tumor initiation, progression, metastasis and drug resistance (15-17). As a key component

of metabolic reprogramming, lipid metabolic dysregulation has been identified as a critical biological feature of gynecological malignancies (18). Beyond providing energy and structural building blocks for rapid tumor cell proliferation, lipid metabolism exerts multifaceted effects on tumor progression through metabolite-mediated signal transduction and tumor microenvironment (TME) remodeling (19). Studies have demonstrated that gynecological cancer cells actively rewire their lipid metabolic networks, encompassing lipid uptake, synthesis, storage and catabolism, to adapt to stressors such as nutrient deprivation and hypoxia within the TME (20,21). Notably, distinct subtypes of gynecological cancers exhibit marked phenotypic heterogeneity in lipid metabolism due to differences in genetic background, etiological factors (for example, obesity association and HPV infection) and TME characteristics (22,23). For instance, obesity-associated endometrial cancer is characterized by sterol regulatory element-binding protein 1 (SREBP1)-driven enhanced lipogenesis, while ovarian clear cell carcinoma (OCCC) is marked by abnormal lipid droplet accumulation and reliance on exogenous fatty acid uptake (24,25). By contrast, HPV-positive cervical cancer displays increased low-density lipoprotein receptor (LDLR)-mediated cholesterol uptake (26). This subtype-specific lipid metabolic reprogramming not only contributes to malignant transformation but also closely associates with therapeutic resistance; for example, platinum-resistant ovarian cancer cells exhibit disrupted cholesterol homeostasis and activated fatty acid oxidation (FAO), while progesterone resistance in endometrial cancer correlates with fatty acid synthase (FASN)-mediated enhanced fatty acid synthesis (27-29).

In recent years, lipid metabolism-targeted therapeutic strategies have emerged as a research focus in oncology. Several inhibitors targeting key lipid metabolic enzymes [for example, FASN, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and stearoyl-CoA desaturase 1 (SCD1)] have advanced to preclinical or early-phase clinical trials, with some demonstrating notable antitumor activity and reversal of drug resistance in gynecological cancer models (30,31). However, significant gaps remain in current research: The subtype-specific regulatory networks of lipid metabolism in gynecological malignancies are not fully elucidated, the crosstalk mechanisms between lipid metabolism and other oncogenic pathways (for example, PI3K/Akt/mTOR and Hippo-YAP) require further investigation, and precision targeting strategies based on lipid metabolic profiles have not been widely translated into clinical practice (32). Therefore, systematically summarizing the subtype-specific features of lipid metabolic dysregulation in gynecological malignancies, elaborating on the underlying molecular regulatory mechanisms, and synthesizing the progress of lipid metabolism-targeted interventions and their clinical translation hold theoretical and clinical importance for advancing precision medicine and improving patient outcomes. The present review focuses on the subtype-specific characteristics of lipid metabolism, core regulatory mechanisms, associations with malignant phenotypes and targeted intervention strategies in gynecological cancers, aiming to provide insights for basic research and clinical translation in this field.

2. Subtype-specific features of dysregulated lipid metabolism in gynecological malignancies

Distinct gynecological malignancies and even different subtypes within the same tumor exhibit marked heterogeneity in lipid metabolic reprogramming patterns (33). This heterogeneity stems from intrinsic differences in genetic background, TME characteristics and etiological mechanisms and exerts a direct impact on tumor biological behavior, therapeutic sensitivity and patient prognosis.

Enhanced FAO and dependence on cholesterol uptake in ovarian cancer. Ovarian cancer encompasses diverse pathological subtypes, among which high-grade serous ovarian cancer (HGSOC), OCCC and endometrioid carcinoma are the three most clinically prevalent subtypes. Each subtype displays distinct divergence in lipid metabolic profiles (34,35). HGSOC accounts for >70% of all ovarian cancer cases, with enhanced FAO as its core metabolic phenotype. Tumor cells adapt to nutrient deprivation and hypoxic stress in the ascites microenvironment by activating the FAO pathway to efficiently utilize fatty acids for energy production (36). Studies have confirmed that the expression of carnitine palmitoyltransferase 1 (CPT1), a key rate-limiting enzyme in FAO, is significantly upregulated in HGSOC cells (37). CPT1 facilitates the translocation of long-chain fatty acids across the mitochondrial membrane and initiates their oxidative breakdown; silencing CPT1 directly inhibits tumor cell proliferation, colony formation and peritoneal metastatic capacity (38). Additionally, HGSOC exhibits aberrant cholesterol uptake: High expression of the LDLR positively correlates with a poor patient prognosis. Serum levels of LDL and total cholesterol in platinum-resistant patients are markedly higher than those in sensitive populations. Enhanced LDLR-mediated exogenous cholesterol uptake may maintain cell membrane stability and reduce drug-induced lipid peroxidation damage, thereby contributing to the development of a resistant phenotype (39,40).

OCCC is characterized by a hallmark feature of abnormal lipid storage: Lipid droplets accumulate extensively within tumor cells, and high expression of the lipid droplet-associated protein adipophilin is correlated with shortened progression-free survival in patients (41). Mechanistic investigations reveal that acyl-CoA cholesterol acyltransferase 1 (ACAT1) is upregulated in OCCC cells, promoting the esterification of free cholesterol for storage in lipid droplets (42,43). This process not only avoids the cytotoxicity of free cholesterol but also enables rapid breakdown for energy supply under nutrient deficiency, conferring a metabolic adaptive advantage. Meanwhile, OCCC cells exhibit low expression of FASN and rely more heavily on exogenous fatty acid uptake, with enhanced CD36-mediated free fatty acid (FFA) transport playing a pivotal regulatory role in tumor proliferation and invasion (44-46).

The endometrioid ovarian cancer subtype shares a strong association with obesity, with enhanced lipogenesis as its core lipid metabolic feature. As a master transcription factor (47), SREBP1 drives the activation of fatty acid synthesis pathways, upregulating the expression of key enzymes such as FASN and acetyl-CoA carboxylase (ACC) (48,49). This promotes *de novo* fatty acid synthesis, providing membrane structural building blocks and energy support for rapid tumor

cell proliferation (50). Collectively, the three major ovarian cancer subtypes exhibit distinct lipid metabolic dependencies: HGSOC relies on FAO-mediated energy production and exogenous cholesterol uptake for survival in the ascites microenvironment; OCCC is characterized by extensive lipid droplet accumulation and dependence on exogenous fatty acid uptake; while endometrioid ovarian cancer shows SREBP1-driven enhanced *de novo* lipogenesis associated with obesity. These divergent metabolic phenotypes directly contribute to their differences in biological behavior, therapeutic sensitivity and patient prognosis.

Enhanced lipogenesis associated with obesity in endometrial cancer. Endometrial cancer is categorized into two subtypes based on etiological features: Type I (estrogen-dependent) and type II (estrogen-independent), and these two subtypes exhibit striking divergence in patterns of lipid metabolic dysregulation. Type I endometrial cancer accounts for ~80% of all endometrial cancer cases and shows a strong association with metabolic syndrome, including obesity, diabetes mellitus and hyperlipidemia (51,52). A core feature of this subtype is enhanced *de novo* lipogenesis as the primary lipid metabolic abnormality. Studies have demonstrated that type I tumors exhibit markedly elevated expression of SREBP1, a master transcription factor that directly binds to the promoter regions of key lipogenic enzymes such as FASN and SCD1, thereby activating *de novo* fatty acid synthesis (53). The hyperestrogenic microenvironment induced by obesity enhances the nuclear localization and transcriptional activity of SREBP1, forming a positive regulatory loop termed the 'estrogen-SREBP1-lipogenesis axis' that continuously drives tumor progression. Additionally, type I endometrial cancer is accompanied by cholesterol metabolic disorders: Upregulated expression of HMGCR promotes endogenous cholesterol synthesis, while statins, by inhibiting HMGCR activity, can markedly suppress tumor cell proliferation and induce apoptosis (54).

Type II endometrial cancer, predominantly composed of serous carcinoma, displays lipid metabolic traits that are distinctly different from those of type I (55). This subtype exhibits substantially enhanced lipid uptake capacity, with upregulated expression of CD36 and fatty acid transport protein 2 (FATP2) enabling efficient scavenging of FFAs from the tumor microenvironment to meet metabolic demands. Concurrently, the level of FAO in type II tumor cells is markedly higher than in type I tumor cells, and increased expression of CPT1A correlates with a poor patient prognosis (56,57). Inhibition of FAO has been shown to enhance the sensitivity of these tumor cells to chemotherapeutic agents. Furthermore, studies have revealed that type II endometrial cancer exhibits reduced expression of ATP-binding cassette (ABC) subfamily A member 1, a protein involved in cholesterol efflux. This downregulation leads to abnormal intracellular cholesterol accumulation, which activates the PI3K/Akt signaling pathway to augment the tumor's invasive and metastatic potential (58-60). In summary, type I and type II endometrial cancers exhibit fundamentally different lipid metabolic profiles: Type I tumors are characterized by SREBP1-mediated enhanced *de novo* lipogenesis driven by obesity and hyperestrogenism, while type II tumors rely on increased lipid uptake and FAO for energy supply. These metabolic differences underlie their distinct responses to hormonal therapy and chemotherapy.

HPV-mediated cholesterol reprogramming in cervical cancer. Cervical cancer development is associated with persistent HPV infection, with HPV16 and HPV18 as the primary high-risk subtypes (61,62). Abnormal lipid metabolism in these tumors is specifically regulated by HPV oncoproteins, featuring a distinct signature centered on cholesterol metabolic reprogramming. Mechanistic studies demonstrate that the HPV E7 oncoprotein upregulates LDLR expression at the transcriptional level while suppressing the transcription of ABC sub-family G member 1, a gene critical for cholesterol efflux. This dual regulation leads to abnormal intracellular cholesterol accumulation, which in turn activates lipid raft-associated c-Src/AKT/FAK signaling pathways to enhance tumor cell migration and invasion (63,64). Additionally, HPV-positive cervical cancer cells exhibit markedly elevated expression of FASN; enhanced fatty acid synthesis driven by FASN promotes lymphangiogenesis, thereby augmenting the potential for lymph node metastasis (65).

Based on histological features, cervical cancer is classified into squamous cell carcinoma and adenocarcinoma subtypes, each with distinct lipid metabolic traits (66,67). Squamous cell carcinoma relies more heavily on FAO for energy production: Upregulated expression of acyl-CoA synthetase long-chain family member 3 (ACSL3) facilitates the activation of long-chain fatty acids and their translocation into mitochondrial oxidative pathways, supplying the energy required for tumor proliferation (68). By contrast, adenocarcinoma is characterized by enhanced lipogenesis, with markedly higher expression of SREBP1 and FASN compared with that in squamous cell carcinoma; targeted inhibition of FASN effectively suppresses its proliferative activity (69). Due to the absence of HPV oncoprotein regulation, HPV-negative cervical cancer exhibits a lipid metabolic pattern analogous to other solid tumors, with enhanced lipid uptake as a core feature. This allows tumor cells to efficiently utilize exogenous lipids to meet their metabolic demands (70-72). Notably, the two major histological subtypes of cervical cancer display divergent lipid metabolic traits: Squamous cell carcinoma depends on ACSL3-mediated FAO for energy production, while adenocarcinoma is characterized by SREBP1-driven enhanced lipogenesis. HPV-negative cervical cancer, lacking the regulation of viral oncoproteins, exhibits a metabolic pattern dominated by enhanced lipid uptake, similar to other solid tumors.

Subtype-specific lipid metabolic features: A comparative summary. To facilitate a clear understanding of the heterogeneous lipid metabolic profiles across gynecological malignancies, a comprehensive table comparing the core metabolic phenotypes, key regulatory molecules, functional impacts and potential targeted agents for each major subtype is presented as Table I.

3. Key links and regulatory networks of abnormal lipid metabolism

Gynecological cancer cells actively rewire their lipid metabolic networks by selectively modulating core processes such

Table I. Subtype-specific lipid metabolic features and potential targeted interventions in gynecological malignancies.

Cancer subtype	Core metabolic phenotype	Key molecules	Functional impacts	Potential targeted agents
Ovarian cancer				
HGSOC	Enhanced FAO + exogenous cholesterol uptake	CPT1A and LDLR	Proliferation, peritoneal metastasis and platinum resistance	Etomoxir and statins
OCCC	Abnormal lipid droplet accumulation + exogenous fatty acid uptake	ACAT1 and CD36	Nutrient stress adaptation and chemoresistance	Avasimibe and VT1021
Endometrioid	SREBP1-driven *de novo* lipogenesis	SREBP1 and FASN	Obesity-associated progression	TVB-2640 and fatostatin
Endometrial cancer				
Type I	SREBP1-driven *de novo* lipogenesis	SREBP1, FASN and HMGCR	Obesity-associated progression and progesterone resistance	TVB-2640 and statins
Type II	Enhanced lipid uptake + FAO	CD36, FATP2 and CPT1A	Invasion, metastasis and chemoresistance	Etomoxir and VT1021
Cervical cancer				
Squamous cell carcinoma	Enhanced FAO	ACSL3 and CPT1A	Proliferation and chemoradiotherapy resistance	Etomoxir
Adenocarcinoma	SREBP1-driven *de novo* lipogenesis	SREBP1 and FASN	Lymph node metastasis	TVB-2640
HPV-negative	Enhanced lipid uptake	CD36 and LDLR	Proliferation and invasion	VT1021 and statins

HGSOC, high-grade serous ovarian cancer; OCCC, ovarian clear cell carcinoma; FAO, fatty acid oxidation; LDLR, low-density lipoprotein receptor; CPT1A, carnitine palmitoyltransferase 1A; ACAT1, acyl-CoA cholesterol acyltransferase 1; SREBP1, SREBP, sterol regulatory element-binding protein 1; FASN, fatty acid synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; FATP2, fatty acid transport protein 2; ACSL3, acyl-CoA synthetase long-chain family member 3; HPV, human papillomavirus.

as lipid uptake, synthesis, storage and catabolism, thereby meeting the demands for malignant proliferation, TME adaptation and therapeutic resistance (73). These abnormally activated metabolic processes are not isolated; instead, they are synergistically regulated by multiple signaling pathways and transcription factors, forming an interconnected and complex molecular regulatory network (74,75).

Core regulation of substrate supply by abnormal lipid uptake and transport. Lipid uptake serves as the initiating and rate-limiting step in tumor cell lipid metabolism. Gynecological cancer cells selectively upregulate the expression and function of lipid transporters to markedly boost the efficiency of exogenous lipid uptake, providing abundant substrates for subsequent metabolic reprogramming and laying a material foundation for malignant tumor progression (76,77).

CD36, a key molecule mediating transmembrane fatty acid transport, is commonly overexpressed in gynecological malignancies such as ovarian and cervical cancer. CD36 specifically mediates the selective uptake of FFAs, particularly unsaturated fatty acids (78). In ovarian cancer, direct contact between omental adipocytes and tumor cells can induce CD36 upregulation in tumor cells via paracrine signaling, enhancing fatty acid uptake efficiency to support energy metabolism during peritoneal metastasis (79). VT1021, a specific CD36 inhibitor, has entered early-phase clinical trials, aiming to inhibit tumor progression by blocking lipid uptake (80).

Abnormal LDLR-mediated cholesterol uptake is one of the key mechanisms underlying platinum resistance in ovarian cancer: Platinum-resistant ovarian cancer cells exhibit markedly elevated LDLR expression, while the expression of HMGCR, a key enzyme in endogenous cholesterol synthesis, is downregulated. This forms a metabolic adaptation pattern characterized by 'enhanced exogenous cholesterol uptake and reduced endogenous synthesis', which maintains cell membrane stability and sustains the resistant phenotype (81,82). Studies have confirmed that silencing tumor necrosis factor receptor-associated protein 1 can mimic this resistant phenotype by upregulating LDLR to enhance cholesterol uptake while suppressing the transcriptional activity of cholesterol synthesis-related genes (83). Additionally, proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to the extracellular domain of LDLR and promotes its intracellular degradation; reduced PCSK9 expression in platinum-resistant ovarian

cancer cells further prolongs the cell membrane residence time of LDLR, boosting its cholesterol uptake efficiency (82).

The FATP family exhibits distinct subtype-specific expression patterns in gynecological cancer: FATP2 is upregulated in ovarian cancer cells, and its specific inhibitor lipofermata can markedly suppress tumor cell proliferation and invasion by blocking long-chain fatty acid uptake. In obesity-associated subtypes of endometrial cancer, FATP1 expression is elevated, which is closely linked to the phenotype of enhanced lipid metabolism and serves as a potential metabolic biomarker for this subtype (84). Fatty acid-binding proteins (FABPs) are responsible for the intracellular targeted transport of lipids. Among them, FABP4 is highly expressed in ovarian cancer, mediating the efficient translocation of lipids from the cell membrane to lipid droplets (85,86). This not only avoids the accumulation of lipid toxicity but also improves the efficiency of tumor cell utilization of TME lipids, providing metabolic support for tumor progression.

Core remodeling of metabolic networks by abnormal lipid synthesis and modification. Enhanced lipogenesis stands as the most distinctive metabolic aberration in gynecological malignancies, primarily involving two core pathways, fatty acid synthesis and cholesterol synthesis, both under the pivotal regulation of the SREBP family of transcription factors (87). Among these, SREBP1 primarily governs fatty acid synthesis and is aberrantly upregulated in gynecological cancers such as endometrial and ovarian cancer. SREBP1 specifically binds to the promoter regions of downstream target genes, activating the transcription and expression of key enzymes, including FASN, ACC and SCD1 (88). As the rate-limiting enzyme in *de novo* fatty acid synthesis, FASN is markedly upregulated in gynecological malignancy, such as cervical cancer (89). FASN catalyzes the condensation of acetyl-CoA and malonyl-CoA to produce palmitic acid, a core building block for tumor cell membrane synthesis and signaling molecule production (90). TVB-2640, a targeted inhibitor of FASN, has demonstrated notable therapeutic activity in HGSOC; when combined with poly(ADP-ribose) polymerase (PARP) inhibitors, it exerts a synergistic effect by suppressing metabolic reprogramming and DNA damage repair, further enhancing antitumor efficacy (91).

SCD1, a key enzyme in fatty acid desaturation, converts saturated fatty acids into monounsaturated fatty acids (MUFAs); its upregulation in ovarian cancer promotes tumor progression by enhancing cell membrane fluidity and attenuating ferroptosis-associated lipid peroxidation (92,93). Inhibition of SCD1 markedly reduces MUFA content in membrane phospholipids, decreases the production of the antioxidant molecule coenzyme Q10, disrupts cellular redox homeostasis, and ultimately induces the accumulation of lipid peroxidation and ferroptosis. A939572, a specific SCD1 inhibitor, has shown promising antitumor effects in preclinical ovarian cancer models, offering a novel direction for the treatment of drug-resistant tumors (94). In the cholesterol synthesis pathway, HMGCR acts as the rate-limiting enzyme; its abnormal expression is closely associated with the malignant progression of cervical and ovarian cancer. Statins, commonly used clinical lipid-lowering agents, can block cholesterol synthesis by inhibiting HMGCR activity, which not only markedly suppresses tumor cell proliferation but also enhances the cytotoxicity of chemotherapeutic drugs, exerting a synergistic therapeutic effect (95).

The aberrant activation of lipid synthesis is further subject to hierarchical regulation by multiple oncogenic signaling pathways (96). Additionally, TP53 mutations can enhance the transcriptional activity of SREBP1 while downregulating the expression of fatty acid degradation-related genes (97,98), leading to abnormal lipid accumulation in ovarian cancer cells and the formation of a metabolic addiction phenotype (99).

Key mechanisms of metabolic adaptation by abnormal lipid storage and catabolism. Lipid droplets serve as core intracellular organelles for lipid storage and metabolic regulation, and exhibit an abnormal accumulation phenomenon in gynecological cancer cells (100,101). The functions of lipid droplets extend beyond mere lipid storage, as they actively participate in regulating tumor progression by dynamically adjusting lipid metabolic balance (102). In ovarian cancer, the expression level of the lipid droplet-associated marker adipophilin is markedly elevated, and this upregulation correlates positively with a poor patient prognosis (103). Inhibitors targeting ACAT1 and HMGCR can block cholesterol esterification and synthesis, respectively, thereby suppressing lipid droplet accumulation in ovarian cancer cells and inhibiting tumor growth. The formation of lipid droplets is associated with cholesterol esterification. ACAT2 is highly expressed in serous ovarian cancer; it converts free cholesterol into cholesterol esters for storage in lipid droplets, thus avoiding the cytotoxicity induced by free cholesterol (104). Lipid droplets form dynamic contact sites with mitochondria to facilitate direct fatty acid transfer for oxidation. This interaction is particularly prominent in cells, supporting their survival under nutrient stress by enhancing FAO efficiency (105,106). The expression level of ACAT2 is positively correlated with chemoresistance in ovarian cancer. Additionally, the phosphatidylcholine synthesis mediated by choline kinase α (CHKα) can promote lipid droplet formation by regulating membrane lipid composition, while dehydrogenase/reductase SDR family member 2 inhibits lipid droplet accumulation and peritoneal metastasis in ovarian cancer cells by downregulating CHKα expression (107,108).

FAO is the core pathway of lipid catabolism and serves an indispensable role in enabling adaptation to the TME and sustaining survival advantages in gynecological cancers (109). Ovarian cancer cells exhibit a distinct feature of enhanced FAO in the ascites microenvironment (110). The translocation of long-chain fatty acids across the mitochondrial membrane, mediated by CPT1, is the rate-limiting step of FAO (111). Etomoxir, a CPT1 inhibitor, can block this process, markedly suppressing the proliferation and survival of ovarian cancer cells under the nutrient-depleted conditions of ascites. Mitochondrial dynamics (fusion and fission) directly regulate FAO efficiency by modulating the assembly of oxidative enzyme complexes. Enhanced mitochondrial fusion in ovarian cancer cells promotes FAO flux and confers chemoresistance, while mitochondrial fission impairs lipid oxidation and induces lipid accumulation (112,113). Studies have confirmed that adipocytes within the ovarian cancer ascites microenvironment secrete FFAs to serve as metabolic substrates for tumor cells (114,115). Tumor cells efficiently utilize these fatty

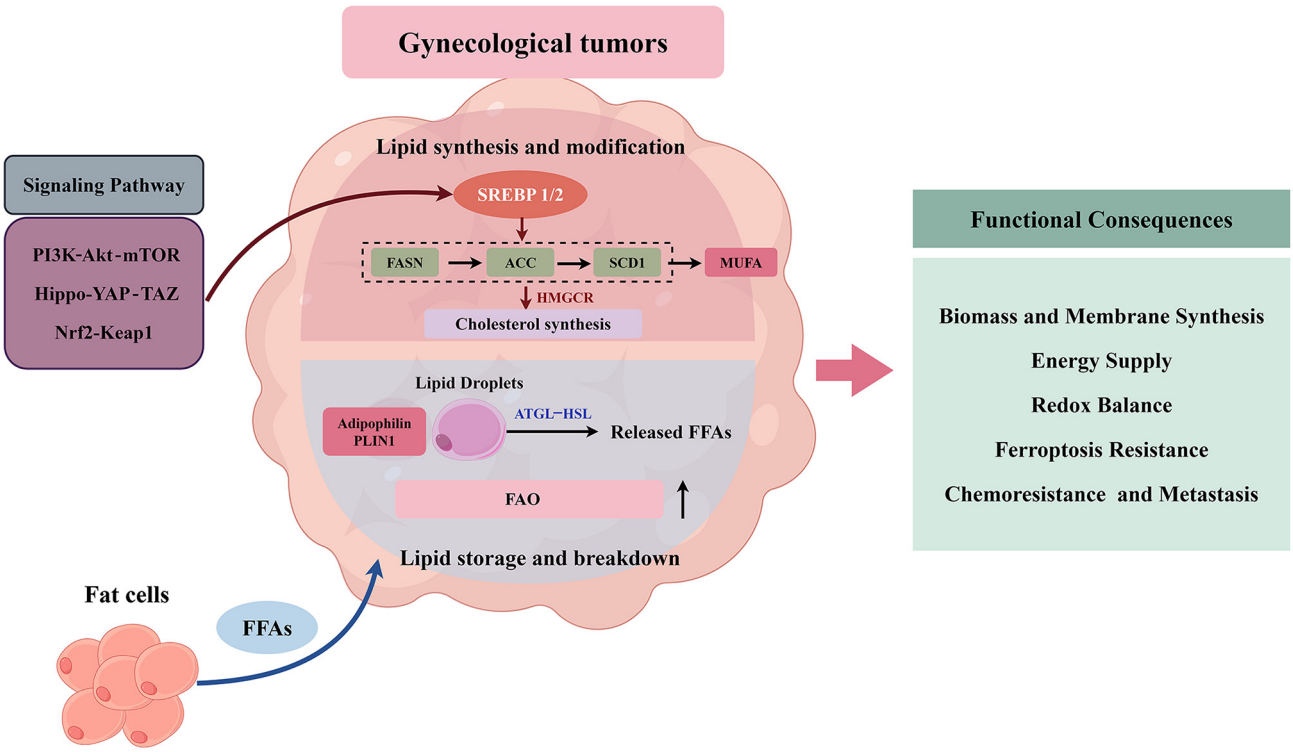

Figure 1. Regulation of lipid metabolic reprogramming and targeted interventions in gynecological malignancies. This figure summarizes the core regulatory networks of lipid metabolic reprogramming in gynecological malignancies, including upstream signaling pathways, key metabolic processes, associations with malignant phenotypes and targeted intervention strategies. Solid arrows indicate direct effects or metabolic flux. FASN, fatty acid synthase; SREBP, sterol regulatory element-binding protein; FAO, fatty acid oxidation; ACC, acetyl-CoA carboxylase; SCD1, stearoyl-CoA desaturase 1; MUFA, monounsaturated fatty acid; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; PLIN1, perilipin-1; ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase; FFA, free fatty acid.

acids by enhancing FAO, while simultaneously activating the AMPK signaling pathway to drive downstream oncogenic signal transduction, forming a vicious cycle of TME lipids-tumor metabolism-signal activation. In endometrial cancer, the upregulated expression of ACSL1 facilitates the activation of long-chain fatty acids and their entry into the FAO pathway, providing sufficient energy for tumor cells. Silencing ACSL1 can significantly inhibit tumor proliferation and metastatic capacity by suppressing FAO activity (116-118).

The dynamic balance between lipid storage and catabolism is dynamically regulated by the nutritional status of the TME. Under nutrient deprivation, tumor cells can rapidly decompose triglycerides and cholesterol esters stored in lipid droplets through lipolysis, releasing FFAs for energy supply. Adipose triglyceride lipase (ATGL) and hormone-sensitive lipase are the core enzymes mediating lipolysis, and both are highly expressed in ovarian cancer (119,120). Inhibiting ATGL can markedly reduce fatty acid release, impairing the survival ability of tumor cells under nutrient-deficient conditions. Furthermore, autophagy (lipophagy) participates in lipid catabolism through the selective degradation of lipid droplets (121). Ovarian cancer cells can activate lipophagy under stress conditions such as hypoxia and nutrient deprivation, converting degraded lipids into energy and metabolic raw materials to provide necessary support for tumor progression (122,123).

Regulatory core of lipid metabolism by signaling pathway crosstalk. The aberrant reprogramming of lipid metabolism is orchestrated by the synergistic regulation of multiple oncogenic signaling pathways, with distinct subtype-specific effects. As a classic oncogenic pathway, the PI3K/Akt/mTOR pathway modulates lipid metabolism via multi-layered, multi-target mechanisms (124,125). Upon activation, it phosphorylates and activates SREBP1, promoting its nuclear translocation and initiating the transcription of lipid synthesis-related genes (126,127). In ovarian cancer, aberrant activation of the PI3K/Akt/mTOR pathway concurrently upregulates the expression of FASN and SCD1, enhancing fatty acid synthesis efficiency while inhibiting the activity of lipolysis-related enzymes (128). This leads to abnormal lipid accumulation, providing both material and energy support for tumor proliferation.

The Hippo-YAP/TAZ pathway directly regulates lipid metabolism by targeting SREBP1 and key metabolic enzymes. YAP/TAZ can bind to the promoter region of SREBP1, facilitating its transcriptional activation and thereby enhancing fatty acid synthesis (129,130). In ovarian cancer cells, aberrant YAP activation upregulates ATP-citrate lyase, which promotes the conversion of citrate to acetyl-CoA, the core precursor for lipid synthesis, while simultaneously boosting the tumor's invasive and metastatic capacity (131,132). Furthermore, YAP regulates the expression of lipid droplet-associated genes (such as perilipin 1), promoting lipid droplet accumulation and strengthening the resistance of tumor cells to chemotherapeutic agents (133).

The Nrf2/Keap1 pathway, a central regulator of cellular oxidative stress (Fig. 1), precisely modulates lipid metabolic homeostasis (134). Activated Nrf2 upregulates the expression of SCD1 and glutathione peroxidase 4 (GPX4), enhancing

tumor cell resistance to ferroptosis through dual mechanisms: Increased MUFA synthesis and suppressed lipid peroxidation. In ovarian cancer, aberrant activation of this pathway is associated with platinum resistance (135,136). Additionally, Nrf2 promotes cholesterol efflux by upregulating ABCG1 expression, maintaining intracellular cholesterol homeostasis and averting cytotoxicity induced by excessive intracellular cholesterol (137,138).

4. Associations between dysregulated lipid metabolism and malignant tumor phenotypes

Dysregulated lipid metabolism in gynecological malignancies is not merely a consequence of metabolic adaptation; instead, it is deeply involved in regulating core malignant phenotypes, including proliferation, metastasis, therapeutic resistance, ferroptosis resistance and immune evasion, through multiple mechanisms such as providing energy substrates, mediating signaling pathway activation, regulating cell death modes and remodeling the tumor immune microenvironment (139,140). This association exhibits distinct tumor subtype specificity, offering clear theoretical basis and therapeutic targets for precision targeted intervention.

Proliferation and metastasis regulated by lipid-mediated signal activation. Aberrant lipid metabolism fuels the malignant proliferation, invasion and metastasis of gynecological cancer cells via the dual mechanisms of 'energy supply-signal regulation' (141). At the level of fatty acid synthesis, palmitic acid generated by enhanced lipogenesis can directly activate the PI3K/Akt signaling pathway, promoting the transition of ovarian cancer cells from the G_1 phase to the S phase of the cell cycle and accelerating proliferation (142). By contrast, FASN inhibitors block this signaling axis by reducing palmitic acid production, arresting tumor cells in the G_1 phase and suppressing proliferative activity. In endometrial cancer, SREBP1-mediated enhanced lipogenesis activates the epithelial-mesenchymal transition process by promoting the degradation of E-cadherin and upregulating the expression of N-cadherin, thereby enhancing the invasive capacity of tumor cells (143,144).

Abnormal cholesterol metabolism, in turn, promotes metastasis by regulating membrane-associated signaling pathways (145). In ovarian cancer cells, enhanced LDLR-mediated cholesterol uptake enriches lipid raft structures in the cell membrane, activating the RhoA/ROCK signaling pathway to facilitate actin cytoskeleton reorganization and improve cell motility and invasiveness (146). In cervical cancer, FASN regulates cholesterol reprogramming to exert dual effects: On the one hand, it activates the lipid raft-associated c-Src/AKT/FAK signaling pathway; on the other hand, it promotes the secretion of platelet-derived growth factor-AA and insulin-like growth factor-binding protein 3, inducing lymphangiogenesis and markedly boosting lymph node metastasis capacity (147). Furthermore, lipid metabolites (for example, oleic acid and cholesterol esters) can upregulate the expression of vascular endothelial growth factor (VEGF) to promote tumor angiogenesis, establishing a nutrient transport network that supports proliferation and metastasis (148,149).

Therapeutic resistance driven by lipid metabolic reprogramming. Lipid metabolic reprogramming serves as a central driver underlying resistance to multiple therapeutic modalities in gynecological malignancies, with distinct subtype-specific metabolic aberrations corresponding to different types of treatment resistance (150,151). For platinum resistance in ovarian cancer, disrupted cholesterol homeostasis plays a pivotal role: Platinum-resistant cells exhibit markedly upregulate LDLR expression, which enhances exogenous cholesterol uptake. This metabolic adaptation maintains cell membrane fluidity and stability, reducing DNA cross-linking damage induced by platinum-based drugs. Statins, by inhibiting HMGCR activity, can lower intracellular cholesterol levels and reverse the platinum-resistant phenotype (152,153). Additionally, FASN-mediated enhanced fatty acid synthesis is linked to PARP inhibitor resistance in ovarian cancer. When the FASN inhibitor TVB-2640 is combined with PARP inhibitors, it exerts a synergistic effect by co-suppressing metabolic reprogramming and DNA damage repair pathways, markedly improving the therapeutic response rate in resistant patients (154-156).

Chemoradiotherapy resistance in cervical cancer is predominantly driven by enhanced FAO; chemoradiotherapy induces upregulated CPT1A expression in cervical cancer cells, activating the FAO pathway to augment energy supply and enhance cell survival under therapeutic stress (157-159). Combining the FAO inhibitor etomoxir with chemoradiotherapy blocks this metabolic adaptation, markedly boosting treatment sensitivity. By contrast, hormone therapy resistance in endometrial cancer is associated with exaggerated lipogenesis: Progesterone-resistant cells display abnormally elevated expression of SREBP1 and FASN (160). Enhanced lipogenesis weakens the growth-inhibitory effect of progesterone by activating the AKT/mTOR signaling pathway, while targeted inhibition of lipogenesis can restore tumor cell sensitivity to progesterone. Mechanistically, lipid metabolic reprogramming mediates drug resistance through three core mechanisms: Augmenting the activity of DNA damage repair enzymes, suppressing the activation of apoptotic signaling pathways and sustaining energy metabolic homeostasis (161-163). Mitochondrial lipid metabolism is a key driver of therapeutic resistance. Enhanced FAO provides sufficient ATP for DNA damage repair and increases mitochondrial antioxidant production. Targeting CPT1A, the rate-limiting enzyme of mitochondrial FAO, effectively reverses platinum resistance in cells (164,165).

Ferroptosis regulation governed by the central regulatory role of lipid metabolism. Ferroptosis is an iron-dependent, lipid peroxidation-mediated form of regulated cell death, and lipid metabolic dysregulation serves as a central regulator in ferroptosis modulation, with this regulatory effect exhibiting distinct tumor subtype specificity (166). SCD1, a key fatty acid desaturase, is upregulated in ovarian cancer (167). The MUFAs catalyzed by SCD1 enhance tumor cell resistance to ferroptosis by decreasing lipid peroxidation accumulation and maintaining cell membrane stability (168). By contrast, SCD1 inhibitors promote ferroptosis induction by increasing polyunsaturated fatty acid (PUFA) accumulation and disrupting redox homeostasis. Studies have confirmed that tumor cells derived

from ovarian cancer ascites show markedly elevated expression levels of SCD1 and fatty acid desaturase 2; combined inhibition of these two enzymes downregulates GPX4 expression, triggering an outbreak of lipid peroxidation and initiating ferroptosis (169-171).

Lipid peroxidation is the core event driving ferroptosis, and intracellular PUFA accumulation markedly enhances lipid peroxidation sensitivity, thereby promoting ferroptosis (172,173). In endometrial cancer cells, upregulated expression of ACSL4 facilitates PUFA activation and integration into membrane phospholipids, increasing the risk of lipid peroxidation (174). Consequently, patients with high ACSL4 expression are more sensitive to ferroptosis inducers. By contrast, lipid droplet accumulation reduces lipid peroxidation by sequestering PUFAs. OCCC, characterized by abundant lipid droplets, exhibits inherent resistance to ferroptosis inducers; targeting diacylglycerol acyltransferase 1, a key gene involved in lipid droplet formation, can diminish the sequestration of PUFAs by lipid droplets, enhancing ferroptosis sensitivity (175). This close association between lipid metabolism and ferroptosis offers a novel direction for gynecological cancer treatment. For instance, the combination of SCD1 inhibitors and cisplatin can enhance the cytotoxicity of cisplatin against ovarian cancer by inducing ferroptosis, thereby improving therapeutic outcomes (176).

Immune microenvironment remodeling mediated by the immunomodulatory role of lipids. Abnormal lipid metabolism shapes an immunosuppressive phenotype by regulating immune cell function and altering the composition of the tumor immune microenvironment, ultimately facilitating tumor immune evasion (177). FFAs secreted by gynecological cancer cells are specifically taken up by tumor-associated macrophages (TAMs), inducing their polarization toward the M2 phenotype. M2-type TAMs suppress effector T-cell function by secreting anti-inflammatory cytokines such as interleukin-10 and transforming growth factor-β. In the ovarian cancer microenvironment, lipid-enriched TAMs also abnormally express programmed death ligand 1 (PD-L1), directly inhibiting the cytotoxic activity of $CD8^+$ T cells via the programmed cell death protein 1 (PD-1)/PD-L1 pathway and impairing the antitumor immune response (178,179).

T-cell function is highly regulated by lipid metabolism: Excess fatty acids in the tumor microenvironment are taken up by $CD8^+$ T cells through CD36-mediated pathways, leading to abnormal intracellular lipid accumulation (180,181). This accumulation inhibits T-cell proliferation and the secretion of cytotoxic molecules (such as perforin and granzyme B), inducing T-cell exhaustion. In cervical cancer, enhanced CD36-mediated fatty acid uptake is a key driver of T-cell exhaustion; combining CD36 inhibitors with PD-1 inhibitors can reduce T-cell lipid accumulation, reverse the exhausted phenotype and markedly enhance antitumor immune efficacy (182,183). Additionally, abnormal lipid metabolism in regulatory T cells (Tregs) contributes to immunosuppression: The fatty acid synthesis pathway in Tregs within the ovarian cancer microenvironment is significantly enhanced, sustaining their survival and immunosuppressive function to weaken antitumor immunity (184,185). Targeting key enzymes in fatty acid synthesis can markedly attenuate the immunosuppressive activity of Tregs and improve the immune microenvironment (Fig. 2).

Tumor cell lipid metabolism abnormalities also regulate immune evasion through other mechanisms: FASN inhibitors can downregulate PD-L1 expression on the tumor cell surface, enhancing the recognition and killing of tumor cells by $CD8^+$ T cells (186,187). Abnormal cholesterol accumulation in ovarian cancer inhibits the infiltration and activity of natural killer (NK) cells, while statins can improve NK cell function by regulating cholesterol metabolism, boosting innate immune responses (188,189).

5. Lipid metabolism-targeted intervention strategies and clinical translation

Given the pivotal role of lipid metabolism in the malignant progression and therapeutic resistance of gynecological malignancies, lipid metabolism-targeted intervention strategies have emerged as a research focus in oncology (190,191). These strategies encompass key metabolic enzyme inhibitors, signaling pathway-targeted agents and multi-modal combination therapies, with several approaches, such as FASN inhibitors and statins, having advanced from preclinical research to clinical translation, providing novel technical pathways and clinical evidence for the precision treatment of gynecological cancer (192,193).

Direct targeting of lipid metabolic processes by key metabolic enzyme inhibitors. Specific inhibitors against key lipid metabolic enzymes represent the most direct intervention strategy. By blocking core processes such as lipid uptake, synthesis and catabolism, these agents disrupt tumor cell metabolic homeostasis to exert antitumor effects. To date, multiple inhibitors have completed preclinical validation in gynecological cancers, with some progressing to clinical trials (194,195).

FASN, the rate-limiting enzyme in *de novo* fatty acid synthesis, serves as a core target for intervention. TVB-2640, a first-in-class oral FASN inhibitor, has completed phase I clinical trials in patients with advanced solid tumors and demonstrated favorable safety and tolerability. Preliminary clinical data show that the combination of TVB-2640 with paclitaxel exhibits promising antitumor activity in patients with recurrent platinum-resistant ovarian cancer (196,197). A phase II clinical trial evaluating its efficacy in combination with bevacizumab for recurrent HGSOC is currently underway, and the results are expected to provide more robust clinical evidence for its application in gynecological malignancies (198). Orlistat, a traditional anti-obesity drug, has been repurposed due to its FASN inhibitory activity. Orlistat exhibits distinct antitumor effects against ovarian and cervical cancer, downregulating FASN expression in cisplatin-resistant cells to impair metabolic adaptation; combination with cisplatin markedly delays tumor progression (199,200).

SCD1 inhibitors exhibit unique advantages in ovarian cancer treatment. Specific inhibitors, such as A939572 and E6446, block SCD1-mediated monounsaturated fatty acid synthesis, promoting polyunsaturated fatty acid accumulation and triggering lipid peroxidation and ferroptosis. These agents significantly suppress tumor growth in ovarian cancer xenograft models, with notable efficacy particularly against

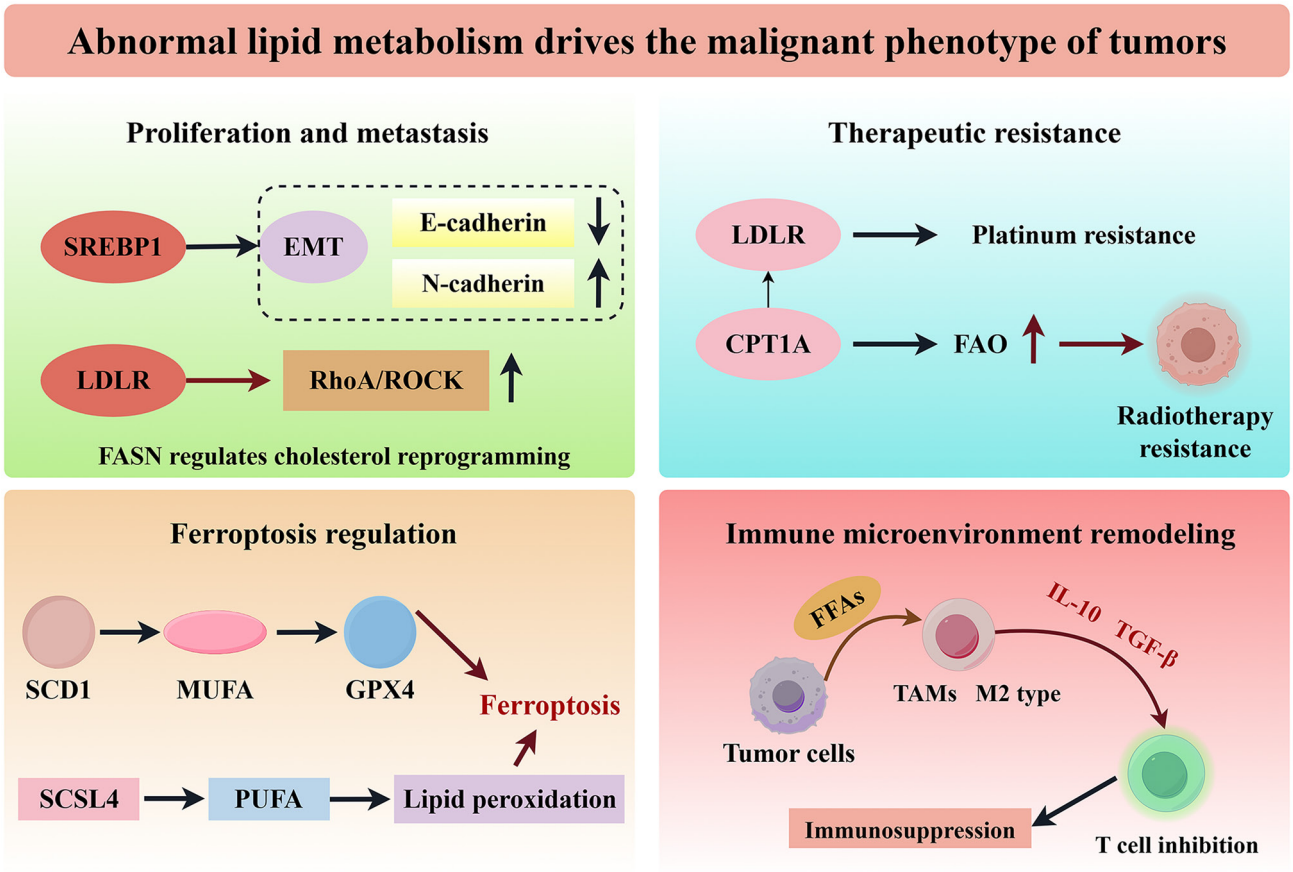

Figure 2. Lipid metabolic dysregulation drives malignant phenotypes of gynecological malignancies: key molecules and regulatory mechanisms. This figure illustrates the core mechanisms by which abnormal lipid metabolism regulates four major malignant phenotypes of gynecological malignancies. Key lipid metabolic molecules (for example, FASN, SCD1, LDLR and CPT1A) and signaling pathways (for example, PI3K/Akt, RhoA/ROCK and PD-1/PD-L1) mediate proliferation and metastasis, therapeutic resistance, ferroptosis resistance, and immune suppression. Solid arrows indicate direct regulatory effects or metabolic flow, while dashed arrows represent indirect modulation. SREBP, sterol regulatory element-binding protein; EMT, epithelial-mesenchymal transition; FASN, fatty acid synthase; SCD1, stearoyl-CoA desaturase 1; LDLR, low-density lipoprotein receptor; CPT1A, carnitine palmitoyltransferase 1A; PD-1/PD-L1, programmed death 1/programmed death ligand 1; FAO, fatty acid oxidation; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; FFA, free fatty acid; TAM, tumor-associated macrophage.

ferroptosis-resistant subtypes (201). HMGCR inhibitors (statins), commonly used as lipid-lowering drugs in clinical practice, have been extensively validated for their antitumor potential: Simvastatin inhibits ovarian cancer cell proliferation and invasion, and enhances chemosensitivity when combined with cisplatin (202). Multiple large-scale epidemiological studies have consistently shown that long-term statin use is associated with reduced incidence of ovarian cancer and improved overall survival in patients with endometrial cancer. Real-world clinical evidence also indicates that statin use combined with platinum-based chemotherapy can prolong progression-free survival in patients with advanced ovarian cancer, particularly in those with high LDLR expression, supporting the potential repurposing value of statins in gynecological cancer treatment (203,204).

Inhibitors targeting FAO are also under active development. Etomoxir, a CPT1 inhibitor, blocks the entry of long-chain fatty acids into the mitochondria, reducing FAO-mediated energy supply and enhancing the sensitivity of gynecological cancer cells to chemotherapy (205). ACAT inhibitors (such as avasimibe and K604) suppress cholesterol esterification and lipid droplet accumulation, exerting antitumor effects by disrupting cholesterol homeostasis in preclinical ovarian cancer models. Additionally, liver X receptor (LXR) agonists (such as GW3965) promote cholesterol efflux and regulate lipid metabolic balance. When combined with anti-VEGF agents, they exert a synergistic effect via 'metabolic regulation-vascular inhibition' enhancing therapeutic outcomes in ovarian cancer (206,207).

Indirect regulation of lipid metabolic networks by signaling pathway-targeted strategies. Drugs targeting lipid metabolism regulatory pathways can indirectly rewire the lipid metabolic networks of tumor cells, thereby achieving antitumor effects. These agents typically modulate core transcription factors or signaling axes to concurrently affect multiple lipid metabolic pathways, featuring a broad range of action and potent synergistic effects.

SREBP pathway inhibitors are core representatives: Fatostatin blocks the activation and nuclear translocation of SREBP, concomitantly suppressing both fatty acid and cholesterol synthesis (208,209). In endometrial cancer, it markedly downregulates the expression of downstream target genes such as FASN and ACC, reduces intracellular lipid accumulation and inhibits tumor growth (210).

PI3K/Akt/mTOR pathway inhibitors indirectly interfere with lipid metabolism by regulating the activation status of

SREBP1. As a VEGF inhibitor, bevacizumab enhances the antitumor efficacy of lipid metabolism inhibitors by indirectly suppressing PI3K/Akt pathway activity. Everolimus, an mTOR inhibitor, directly inhibits lipid synthesis in ovarian cancer cells and exerts a synergistic antitumor effect when combined with FASN inhibitors (211,212).

Hippo-YAP/TAZ pathway inhibitors exert their functions by regulating lipid metabolic networks: Verteporfin, a YAP inhibitor, downregulates SREBP1 expression, inhibits fatty acid synthesis and lipid droplet accumulation in ovarian cancer cells, and concomitantly impairs the chemoresistance of tumor cells (213,214). Inhibitors of Nrf2, such as ML385, disrupt cellular redox homeostasis by suppressing the Nrf2/Keap1 pathway, increasing lipid peroxidation levels and promoting ferroptosis. When combined with SCD1 inhibitors, they markedly enhance the therapeutic efficacy against ovarian cancer through the combined effect of metabolic inhibition and oxidative stress (215,216).

Combined efficacy and resistance reversal by combination therapy regimens. Single-agent targeted therapy against lipid metabolism often yields limited effects, making multi-modal combination therapy an emerging core direction to break treatment bottlenecks and reverse drug resistance (217). By combining lipid metabolism inhibitors with chemotherapy, targeted therapy or immunotherapy, synergistic efficacy can be achieved through mechanism complementarity, while simultaneously covering tumor cell populations with diverse metabolic phenotypes (218,219).

The combination of lipid metabolism inhibitors and chemotherapy effectively reverses metabolism-adaptive resistance. For instance, the combination of SCD1 inhibitors and cisplatin enhances cisplatin-induced DNA damage by inducing ferroptosis, reversing platinum resistance in ovarian cancer (220). Statins combined with paclitaxel strengthen the cytotoxicity of chemoradiotherapy in cervical cancer by inhibiting cholesterol synthesis, thereby improving treatment sensitivity. Mechanistically, such combinations regulate lipid metabolic balance, promote the accumulation of drug-induced DNA damage and activate apoptotic signaling, breaking the metabolic adaptive advantage of tumor cells (221,222).

The combination of lipid metabolism inhibitors and immunotherapy represents a highly promising approach. FASN inhibitors downregulate the expression level of PD-L1 on tumor cell surfaces, reducing immune checkpoint-mediated immune evasion; when combined with PD-1 inhibitors, they enhance the cytotoxic activity of $CD8^+$ T cells and markedly improve therapeutic outcomes in ovarian cancer (223,224). CD36 inhibitors combined with PD-L1 inhibitors reduce lipid accumulation and exhaustion in T cells, remodel the cervical cancer immune microenvironment and exhibit synergistic antitumor activity (225). Additionally, LXR agonists improve the polarization phenotype of TAMs by promoting cholesterol efflux, thereby boosting the antitumor effects of immunotherapy (226,227).

The combination of lipid metabolism inhibitors and PARP inhibitors targets the 'metabolic reprogramming-DNA damage repair' pathway. The combination of TVB-2640 and PARP inhibitors enhances the synthetic lethal effect induced by PARP inhibitors by suppressing fatty acid synthesis, markedly improving the therapeutic response rate in HGSOC (228,229). A preclinical study demonstrated that this combination effectively inhibits the proliferation of drug-resistant cells and extends the survival time of tumor-bearing mice, providing a novel therapeutic option for tumors with abnormal DNA damage repair pathways (230).

Clinical translation progress from basic research to clinical application. Lipid metabolism-targeted intervention strategies have achieved phased progress in clinical translation, with multiple agents advancing to clinical trials at various stages, and a biomarker-guided precision treatment model taking shape.

The clinical translation of the FASN inhibitor TVB-2640 has been notable: Phase I clinical trials have confirmed its favorable safety and tolerability in patients with advanced solid tumors, with partial disease remission observed in some cases (231-233). A phase II trial is evaluating its efficacy in combination with bevacizumab for recurrent high-grade astrocytoma, providing valuable reference data for analogous combination therapies in gynecological malignancies (234,235). Statins demonstrate distinct advantages in clinical translation: Numerous epidemiological studies have linked statin use to a reduced incidence risk of ovarian and endometrial cancer (236). A phase II clinical trial is assessing the efficacy of atorvastatin combined with progestogens in early-stage endometrial cancer, and preliminary findings indicate that this combination regimen markedly reduces tumor Ki-67 proliferation index (237). A separate phase II trial investigating rosuvastatin + progestogens for early-stage endometrial cancer is also underway to validate the feasibility and safety of this regimen as fertility-sparing therapy, with preclinical mechanistic evidence supporting the biological rationale for this combination strategy (238).

Overall, biomarker-guided precision targeted therapy has emerged as the core direction for future development. Lipid metabolism-related molecules, including FASN, fatty acid transporter CD36 and LDLR, have been validated as prognostic biomarkers and predictors of treatment response. Studies have found that patients with ovarian cancer with high FASN expression are more sensitive to TVB-2640 treatment, while patients with cervical cancer with elevated CD36 expression are more likely to benefit from the combination of CD36 inhibitors and immunotherapy. Future clinical research should further expand sample sizes to validate the clinical predictive value of these biomarkers, establish a precision treatment decision-making system based on lipid metabolic profiles, and realize individualized therapy centered on metabolic subtyping and targeted intervention. Several lipid metabolism-related biomarkers have been validated in clinical settings for prognostic prediction and treatment response stratification. For example, high FASN expression in tumor tissues is an independent poor prognostic factor for ovarian cancer and predicts better response to TVB-2640 treatment. Serum LDL cholesterol levels have been shown to correlate with platinum resistance in patients with ovarian cancer. Additionally, CD36 expression in tumor-infiltrating $CD8^+$ T cells predicts the efficacy of anti-PD-1 immunotherapy in patients with cervical cancer, providing a potential

biomarker for patient selection and individualized treatment decision-making.

6. Challenges and future perspectives

Compared with previously published reviews focusing on a single tumor type or general lipid metabolic phenotypes, the present review provides a subtype-centric systematic overview across three major gynecological malignancies. The review integrates a full regulatory axis from upstream oncogenic signaling to downstream malignant phenotypes, incorporates emerging mechanisms of ferroptosis regulation and immune microenvironment remodeling, and further summarizes the clinical translation progress of subtype-matched targeted interventions. This aims to offer a more refined theoretical framework for precision metabolic intervention in gynecological malignancies. While this review systematically summarizes the subtype-specific lipid metabolic reprogramming mechanisms and emerging targeted intervention strategies in gynecological malignancies, several critical evidence gaps remain that limit the clinical feasibility of current research plans. Most mechanistic insights are derived from preclinical cell line and animal models, which cannot fully recapitulate the complexity of the human tumor microenvironment and interpatient metabolic heterogeneity. Large-scale, subtype-enriched clinical trials are still lacking to validate the efficacy and safety of lipid metabolism-targeted therapies, and there is no standardized biomarker system to guide patient selection and dynamic efficacy monitoring.

Building on these limitations, despite the groundbreaking advancements in lipid metabolism-targeted research, its clinical translation and widespread application in gynecological malignancies face multiple interconnected challenges that require systematic investigations to address (239). First, the network complexity of lipid metabolism and tumor subtype specificity represent the core constraint for targeted therapy. Notable heterogeneity in lipid metabolic profiles exists across distinct gynecological cancer subtypes and even among patients within the same subtype (240). For instance, the serous subtype of ovarian cancer is characterized by enhanced FAO, while the clear cell subtype relies on lipid storage and exogenous uptake (241). A single therapeutic regimen struggles to cover all metabolic phenotypes, hampering the implementation of precision intervention. Second, the insufficient target specificity of lipid metabolism inhibitors poses a critical issue. Lipid metabolism is a fundamental physiological process in normal cells, and existing inhibitors cannot fully distinguish the metabolic differences between tumor and normal cells. This tends to disrupt lipid homeostasis in normal tissues (such as liver and adipose tissues), leading to off-target effects and adverse reactions. For example, statins may induce muscle injury, while FASN inhibitors can cause weight loss and metabolic disorders (242). Additionally, extensive crosstalk between metabolic pathways increases the risk of therapeutic resistance (243). Lipid metabolism is intricately regulated through cross-talk with glucose metabolism, amino acid metabolism and oncogenic signaling pathways. Targeting lipid metabolism alone is prone to inducing tumor cells to switch their metabolic dependency via reprogramming (for example, shifting from lipogenesis to glycolysis), resulting in adaptive therapeutic resistance and compromised long-term efficacy (244,245).

Future research should focus on the following core directions to optimize and advance lipid metabolism-targeted strategies: i) Systematically decipher the subtype-specific regulatory networks of lipid metabolism in gynecological malignancies. Integrate multi-omics technologies (for example, transcriptomics, lipidomics and metabolomics) with single-cell sequencing to identify subtype-specific and patient-specific metabolic targets, providing a molecular classification basis for precision therapy. ii) Develop highly selective lipid metabolism inhibitors and leverage novel drug delivery systems (such as liposomes and polymeric nanoparticles) to achieve tumor-specific drug accumulation. This approach can minimize damage to normal tissues while improving drug bioavailability and tumor penetration. iii) Elucidate the cross-talk mechanisms between lipid metabolism and oncogenic pathways such as PI3K/Akt/mTOR and Hippo-YAP. Develop multi-targeted combination therapy regimens that exert dual effects of 'metabolic inhibition + signal blocking' to overcome therapeutic resistance caused by single-target interventions. iv) Identify and validate lipid metabolism-related biomarkers (for example, FASN, CD36 and LDLR) through multi-center, large-cohort studies. Establish individualized treatment prediction models incorporating metabolic features and clinicopathological parameters to guide treatment selection and dynamic efficacy assessment. v) Conduct subtype-enriched clinical trials targeting specific populations (such as HGSOC and obesity-associated endometrial cancer). Validate the efficacy, safety and dosage optimization of lipid metabolism-targeted therapies to expedite their clinical translation.

With the in-depth elucidation of lipid metabolism regulatory mechanisms in gynecological malignancies, lipid metabolism-targeted strategies are expected to become an integral component of precision therapy for these diseases. They may provide a novel breakthrough for improving the prognosis of advanced and drug-resistant patients, ultimately achieving the closed-loop of metabolic subtyping-precision intervention-efficacy prediction in individualized therapy.

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Authors' contributions

YR conceived the study, conducted the systematic literature retrieval and screening, extracted the relevant research data, drafted the full manuscript and critically revised it. Data

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that they have no competing interests.

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