REVIEW

Lipid metabolism reprogramming in endometrial cancer: biological functions and therapeutic implications

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Abstract

Background Endometrial cancer is one of the major gynecological cancers, with increasing incidence and mortality in the past decades. Emerging preclinical and clinical data have indicated its close association with obesity and dyslipidemia. Metabolism reprogramming has been considered as the hallmark of cancer, to satisfy the extensive need of nutrients and energy for survival and growth. Particularly, lipid metabolism reprogramming has aroused the researchers' interest in the field of cancer, including tumorigenesis, invasiveness, metastasis, therapeutic resistance and immunity modulation, etc. But the roles of lipid metabolism reprogramming in endometrial cancer have not been fully understood. This review has summarized how lipid metabolism reprogramming induces oncogenesis and progression of endometrial cancer, including the biological functions of aberrant lipid metabolism pathway and altered transcription regulation of lipid metabolism pathway. Besides, we proposed novel therapeutic strategies of targeting lipid metabolism pathway and concentrated on its potential of sensitizing immunotherapy and hormonal therapy, to further optimize the existing treatment modalities of patients with advanced/metastatic endometrial cancer. Moreover, we expect that targeting lipid metabolism plus hormone therapy may block the endometrial malignant transformation and enrich the preventative approaches of endometrial cancer.

Conclusion Lipid metabolism reprogramming plays an important role in tumor initiation and cancer progression of endometrial cancer. Targeting the core enzymes and transcriptional factors of lipid metabolism pathway alone or in combination with immunotherapy/hormone treatment is expected to decrease the tumor burden and provide promising treatment opportunity for patients with advanced/metastatic endometrial cancer.

Keywords Endometrial cancer, Lipid metabolism reprogramming, Tumorigenesis, Cancer progression, Targeted therapy

Background

Endometrial cancer (EC) has become one of the most prevalent gynecological malignancies with 420, 242 newly diagnosed and 97,704 death patients worldwide

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[1]. Due to lifestyle risk factors like obesity and the lacking of treatment advancement, the incidence and mortality of EC have continued to rise for decades, directly threatening females' health and survival [2, 3]. Surgery alone or combined with radiation and/or platinum-based chemotherapy as well as hormone therapy can generate good efficacy in most EC patients [4]. However, the 5-year survival rates of patients with stage III/IV tumors remain only 48% and 15% respectively [5]. What's worse, the median overall survival (OS) of recurrent/metastatic patient is extremely short, ranging from 12 to 15 months

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[6]. Recently, adjuvant immunotherapy therapy has provided extra treatment opportunity for advanced and metastatic EC patients, but there is ultimately unmet need in the management of almost half of mismatch repair deficient EC and the majority of mismatch repair proficient EC that include copy-number low and copy-number high (P53 mutant) tumors [7, 8]. Thus, it's necessary to further explicit the biological mechanism of cancer progression, and identify corresponding new therapeutic strategies in EC.

EC is a metabolism disorders-related malignancy [9–12]. Until now, over 50% of EC may be attributed to obesity [3]. Besides, obesity is related to earlier age at diagnosis of EC, suggesting its role in accelerating tumorigenesis [13]. Adipose tissues not only contribute to a proinflammatory microenvironment, but also produce overloaded estrogen, both contributing to the risk of endometrial cancer [4]. Remarkably, dyslipidemia is an independent predictor of endometrial cancer, which promotes the tumorigenesis through obesity [14]. The traditional clinicopathological classification of EC is associated with metabolic risk factors. Bokhman divided EC into two subgroups: Type I tumors are mainly endometrioid, characterized by obesity, hyperglycemia, hyperlipidemia and hyperestrogenism, sensitive to hormone therapy, frequently > 50 years old, with favorable prognosis; Type II tumors are almost serous, insensitive to hormone treatment, usually < 50 years old, with worse clinical outcomes [15]. A large-sample epidemiological research has demonstrated metabolism risk factors like obesity, previously linked to type I EC are also significantly associated with the incidence risk of more aggressive type II EC [16], indicating the metabolic disturbance in tumor progression. In consistent with this, there was a significant increasing trend of the mortality risk in overweighted or obese EC patients [17]. Actually, obesity is the intersection of complex biological processes.

Metabolism reprogramming has been recognized as the hallmark of cancer. Metabolism network was rearranged to induce the transformation of normal cells, and to promote the division of tumor cells in nutrient-depleted conditions [18]. Metabolic adaption also affected the tumor immunity and promote metastasis [19–21]. Tumor cells tended to exploit glycolysis even in aerobic microenvironment, called the "Warburg effect", which is rewired by tumorigenic mutations in key genes like *TP53* and *KRAS*. Tumoral glycolysis will provide necessary metabolites for lipid synthesis and regulating lipid metabolism pathway [22]. Lipid plays a pivotal role in oncological biology, including serving as constitutional component of cellular bio-membrane, fueling cell growth and mediating signaling transduction, etc [23]. Lipid metabolism reprogramming involving carcinogenesis, invasiveness, metastasis,

therapy resistance and immunity of cancer has greatly drawn the researchers' attention [24–26].

Therefore, we will concentrate on the biologic functions of lipid metabolism reprogramming and aberrant transcriptional regulation of lipid metabolism pathway in endometrial cancer. Importantly, we'll propose the therapeutic strategies of targeting lipid metabolism pathway and summarize ongoing development of agents under preclinical and clinical assessment, in an attempt to renew the current intervention landscape of EC patients.

The biological functions of lipid metabolism reprogramming in endometrial cancer
Altered lipid uptake promoting tumor proliferation and progression
Abnormal fatty acid uptake
Fatty acid (FA) involves in cellular membrane structure, energy production and signal transduction [27]. Exogenous FAs serve as an important source of cancer cell growth, dependent on the transportation of several membranous proteins, including CD36, fatty acid transport protein (FATP) and fatty acid binding protein (FABP) [28] (Fig. 1).

It's reported that CD36 can promote FA uptake via endocytosis mediated by palmitoylation [29]. CD36 was generally upregulated in cancer and could promote tumor growth, metastasis and resistance [30, 31]. CD36 deletion attenuated the liver metastasis of cancer in mice model [32]. Besides, metabolism reprogramming mediated by CD36 induced tumor resistance to anti-HER2 therapy in breast cancer [33]. In pancreatic ductal adenocarcinoma, the expression of CD36 led to gemcitabine-resistant tumor by regulating anti-apoptotic protein [34]. Su et al [35] reported, visceral obesity and metabolic syndrome were directly associated with EC. Adiponectin inhibited the expression of its targeted gene CD36 via downregulating the transcriptional activity of STAT3 signaling, thus reducing peroxisome proliferator-activated receptor (PPAR) activity and suppressing adipocyte differentiation. In contrast, Knapp et al [36] found in grade I, FIGO I endometrioid EC, FA transporters (CD36 and FATP1) were expressed significantly lower than glucose transporter, indicating that CD36 dependent FA uptake may not serve as the main energetic source in early stage, low grade of EC when glucose can be efficiently supplied. But the specific mechanisms of this metabolic switch in EC have not been fully understood. Though some debates seem still existing, the expression and effect of CD36 in glucose-depleted EC will stimulate the research activity.

FABP is able to bind to ligands like long chain FAs. Some literatures reported the dysregulated expression of FABPs facilitated tumor progression [37]. FABP was overexpressed in colon cancer tissue with enhanced
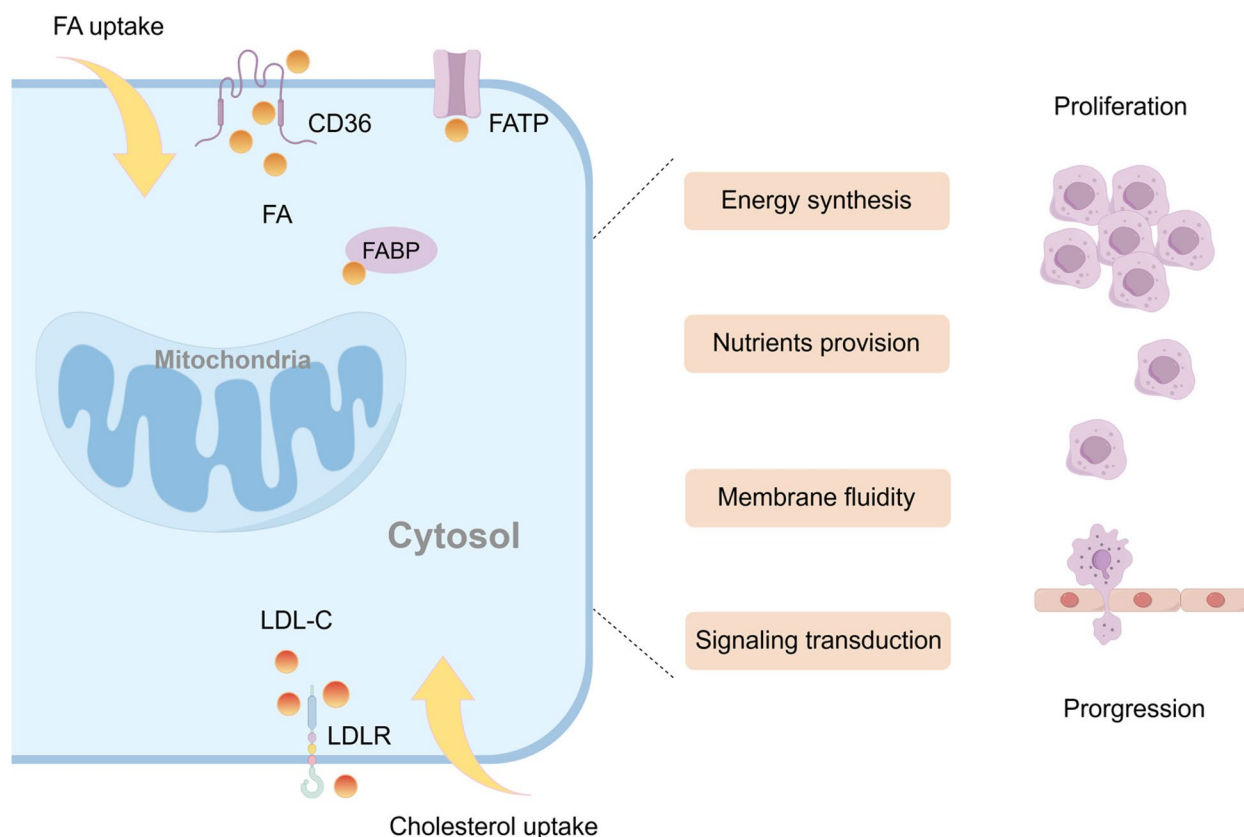
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Fig. 1 Lipid uptake and its biological effects in endometrial cancer. FA, fatty acid; FABP, fatty acid binding protein; FATP, fatty acid transportation protein; LDL-C, low-density lipoprotein-cholesterol; LDLR, low-density lipoprotein receptor (By Figdraw)

lipids accumulation, and promoted the invasiveness and migration by activating AKT pathway and epithelial-mesenchymal transition (EMT) [38]. Also, the upregulation of FABP5 was observed in liver carcinoma, which drove tumor growth via the activation of PI3K/AKT pathway [39]. Moreover, obese breast cancer patients showed significant higher level of circulating FABP, probably because free FABP released from fat tissues stimulated IL-6/STAT3/ALDH signaling pathway, further potentiating cancer cell stemness and invasion [40]. In EC, mass immune blot and immunohistochemistry both indicated significantly increased epidermal FABP (FABP5), in line with spectrometry analysis [41]. Another study demonstrated that compared to normal endometrium and endometrial intraepithelial neoplasia, FABP5 was significantly higher and associated with enhanced immune responsiveness and worse histodifferentiation in EC [42]. However, FABP4 protein and mRNA were reduced in EC. The overexpression of FABP4 exerted inhibitory effect in tumor growth and metastasis by blocking the activation of PI3K/AKT pathway [43], so FABP4 may serve as a tumor suppressor. In short, different subtypes of FABPs have distinct biological effects in EC, which may be the candidate therapeutic target and prognostic biomarker. How to regulate certain isoform of FABPs precisely may be the major challenge in treatment development.

Abnormal cholesterol uptake

Cholesterol belongs to sterols, as an essential constitutional component of cellular membrane, involved in signaling transduction and biosynthesis [44, 45]. Activated cholesterol uptake was usually observed in proliferative cancer cells. Low-density lipoprotein receptor (LDLR) is a single-transmembrane protein, mediating low-density lipoprotein-cholesterol (LDL-C) into cancer cell and maintaining cholesterol homeostasis [46, 47] (Fig. 1). The expression of LDLR and LDL-C were abnormally increased, and the former was an independent prognostic factor in some malignancies [47]. Previous research demonstrated that hypercholesterolemia contributed to the tumor growth and silencing LDLR reversed the tumor-promoting effect [48]. A Mendelian randomization study showed elevated LDL-C can predict good prognosis in EC, including both endometrioid and non-endometrioid tumors [49]. More importantly, after excluding possible mixed effects of obesity, LDL-C was still significantly

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related to reduced risk of incidence in EC, especially non-endometrioid diseases [49]. In EC, though the tumor inhibitory effect of LDL-C has been approved, accessible data of LDLR in tumor occurrence and patients' prognosis are quite limited. So, the definite expression level of LDLR should be determined to better explain the involvement of cholesterol uptake process in EC.

FA and cholesterol uptake can not only provide exogeneous energy for tumor growth and proliferation, but also promote tumor invasiveness and migration by signaling transduction. Though many studies have proved enhanced lipid uptake represents unfavorable outcome in a variety of cancers, some studies have reported its contradictory effects in endometrial cancer. As we know, EC is a malignant tumor with lipid metabolism disorder. More basic and clinical studies are required to clarify whether endometrial cancer has a unique relation to lipid uptake dysregulation.

Aberrant *de novo* lipogenesis facilitating tumor growth and metastasis

Despite the dependence of exogenous lipid uptake, endogenous lipid *de novo* synthesis account for major lipid provision in cancer cell. Lipid biosynthesis mainly contains the synthesis of FA, cholesterol and phospholipid. As the key substrate for FA and cholesterol generation, acetyl-CoA was produced with the catalyzation of ATP-citrate lyase (ACLY) and acetyl-CoA synthetase 2 (ACSS2) [50, 51]. FA production requires acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN), and monounsaturated fatty acid (MUFA) was then produced by stearic acid desaturase (SCD) [28]. Cholesterol was synthesized by 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR) and squalene monooxygenase (SM), further esterified into cholesteryl ester by acyl CoA: cholesterol acyltransferase (ACAT). Moreover, phospholipid was synthesized with CTP: phosphocholine cytidylyltransferase catalyzation and phospholipid remodeling was catalyzed by lysophosphatidylcholine acyltransferase. Potentiated lipid synthesis has been considered to promote tumor generation and progression, so comprehensively exploring the influence of disturbed lipid synthesis pathway and related key enzymes expression on tumor development in EC, will be beneficial to predict patients' prognosis and identify novel hallmarks and therapeutic targets of EC (Fig. 2).

Enhanced acetyl-CoA biosynthesis

Acetyl-CoA is at the core of cancer metabolism, which plays a critical role in FA and cholesterol synthesis, and histone acetylation, thus affecting the proliferative and invasive ability of cancer cell [52]. ACLY could drive transformation of citrate into acetyl-CoA, linking three major nutrients catabolic pathways to lipid biosynthesis [53]. ACLY was highly expressed in malignant tumors and can be an independent predictor of cancer recurrence risk [54–56]. Additionally, various mechanisms-induced ACLY upregulation has strongly promote the stemness and/or progression in colon cancer and breast cancer [57–59]. In contrast to this, downregulating ACLY would reduce intracellular lipid synthesis and accumulation by the ubiquitination and degradation of PPARγ, a transcriptional regulator of lipid metabolism pathway [60]. What's more, acetyl-CoA can epigenetically regulate cancer cell proliferation via histone acetylation. Dai et al [61] found that ACLY mRNA and protein were both hyper-expressed in EC and were obviously correlated to some malignant clinicopathological characteristics and relatively higher BMI. Moreover, following mechanism exploration indicated AKT contributed to tumor cell proliferation via the intracellular nucleus translocation of ACLY, to potentiate histone acetylation and the expression of pyrimidine metabolism genes (like DHODH). Caspase-10 could inhibit acetyl-CoA synthesis by decomposing ACLY, and simultaneously decrease lipid and histone acetylation, effectively suppressing tumor proliferation and metastasis [62]. Thus, ACLY may elicit tumor-stimulatory effects by activating acetyl-CoA production through directly activating downstream lipid metabolism and other mechanisms like epigenetic regulation of DNA biosynthesis in EC.

In recent years, ACSS has been increasingly reported to capture cytoplasmic acetate as a carbon source in cancer, particularly in condition of ACLY genetic deletion or metabolic stress [51, 63, 64]. Among ACSS family members, the oncological biofunction of ACSS2 in cancer has been better described [65]. ACSS2 overexpression was observed in some solid tumor, including breast cancer, liver cancer and prostate cancer, predicting patients' negative prognosis [66]. ACSS2 can also mediate histone acetylation to augment tumorigenesis. In particular, ACSS2 was highly expressed in obese myeloma patients, and prompted interferon regulator 4 (oncogene) mediated gene transcription by activating acetylation. At the same time, ACSS2 inhibition suppressed tumor growth in obese mouse model [67], indicating that ACSS2 may also play an important role in other obesity-induced tumors, especially EC.

The upregulation of acetyl-CoA synthesis pathway, featured by activated key enzymes like ACLY, is linked to cancer progression of obese malignant tumors and EC, which can fuel tumor growth and metastasis via stimulating acetylation and driving the downstream lipid anabolism pathway. Due to this, key enzymes in acetyl-CoA production will be potential target for EC with unbalanced lipid metabolism.
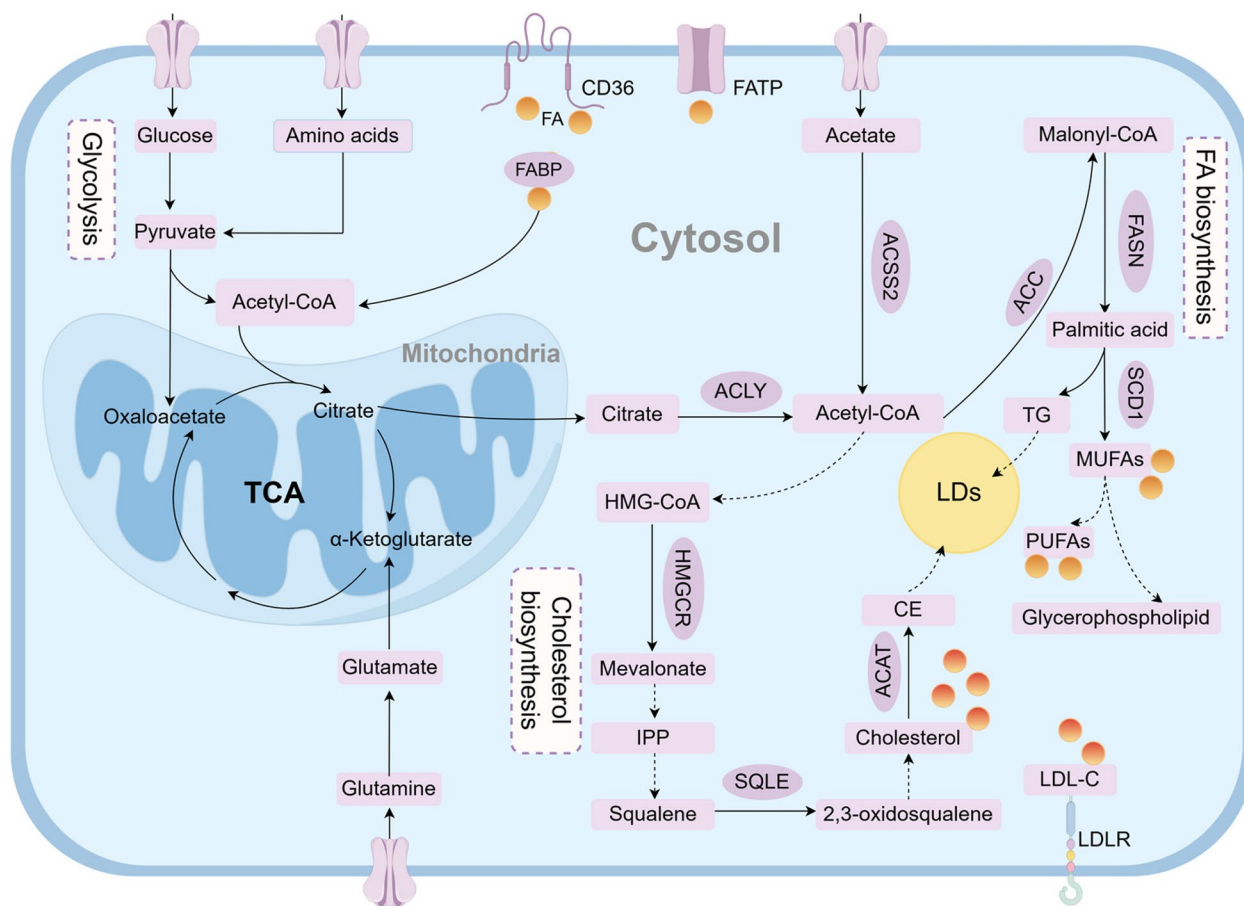
Fig. 2 FAs and cholesterol provision in endometrial cancer. Lipid provision in endometrial cancer includes cellular uptake of exogeneous lipids and intracellular lipid synthesis. Fatty acid uptake is mediated by CD36 and fatty acid transport (FATP) and cholesterol is absorbed by low-density lipoprotein receptor (LDLR) in the form of low-density lipoprotein-cholesterol (LDL-C). Acetyl-CoA is the central metabolic source for de novo lipogenesis, which is mainly derived from citrate produced in tricarboxylic acid (TCA) cycle by ATP-citrate lyase (ACLY) catalyzation, thus closely linking the three major nutrients metabolism pathways to downstream lipid metabolism pathway. Also, acetyl-CoA is partly converted from cytoplasmic acetate with acetyl-CoA synthetase 2 (ACSS2) involvement, especially under the condition of ACLY deletion or metabolic stress. FAs and cholesterol are synthesized with acetyl-CoA, under the control of key enzymes. On one hand, Acetyl-CoA is catalyzed by acetyl-CoA carboxylase (ACC) to produce malonyl CoA. Then, palmitic acid is synthesized by fatty acid synthase (FASN), and subsequently desaturated to monounsaturated fatty acid (MUFA) by stearic acid desaturase 1 (SCD1). MUFAs can be further transformed to PUFAs and/or used to generate glycerophospholipids. On the other hand, HMG-CoA is synthesized with acetyl-CoA and acetoacetyl-CoA, then to produce mevalonate by 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR) catalyzation. Squalene is converted to 2,3-oxidoaualene with SQLE involvement, to produce cholesterol after some steps. In particular, palmitic acid participates in triglyceride (TG) formation and cholesterol is esterified by acyl CoA: cholesterol acyltransferase (ACAT) to CE. Both TG and cholesteryl ester (CE) can be stored in lipid droplets (LDs) (By Figdraw)

Potentiated FA biosynthesis

Acetyl-CoA being converted to malonyl CoA by ACC is the first and speed-limiting step in FA synthesis pathway. Then, acetyl-CoA added to malonyl CoA by FASN is to generate long chain saturated FA (or called palmitate), which will be desaturated to monounsaturated fatty acid (MUFA) by stearoyl-CoA desaturase [68].

ACC is divided into ACC1 and ACC2. ACC1 is located in cytoplasm, responsible for FA synthesis while ACC2 is situated at mitochondrial outer-membrane, mainly regulating FA uptake and β-oxidation [69]. ACC can enhance FA synthesis to provide needy energy for tumor cell survival and growth. Adenosine monophosphate activates protein kinase (AMPK) mediated dysregulated ACC1 and ACC2 phosphorylation may potentiate fat accumulation and cell proliferation [70]. Compared to the healthy tissues, the expression levels of ACC1 and ACC2 were increased in EC tissues [71]. Modesitt et al [72] found that in EC tissue of obese women, the inhibitory phosphorylation of ACC by AMPK was reduced with hepatic kinase B1 at a low level, partly explaining the enhanced fat production in these patients. These studies suggest

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that increased expression/activity of ACC can promote the cancer cell growth through activating FA biosynthesis, which is likely to be associated with obese EC. But direct proofs concerning the influences of ACC overexpression on cancer invasion and metastasis should be provided, and whether ACC can serve as a targetable molecule also requires further exploration in EC.

FASN took control of cancer cell viability and growth by synthesizing FA [73]. In EC, the expression and function of FASN have drawn much attention. It's reported that the expression level of FASN gradually increased with disease progression as benign endometrium hyperplasia and endometrial dysplasia developed into EC [74]. FASN was expressed in most endometrioid adenocarcinoma and closely associated with the ability of tumor invasiveness and metastasis as well as higher BMI [75], which may independently predict the recurrence risk of EC [76]. Moreover, the overexpression of FASN tends to strengthen the carcinogenicity of EC. FASN expression was upregulated by SNHG25 and RAC3, facilitating the tumoral proliferation, invasiveness and migration [77, 78], while FASN inhibition might induce apoptosis of Ishikawa cell line [79]. In term of this, FASN upregulation is likely to accelerate malignant transformation of endometrium and aggressive biological behaviors, and can be an unfavorable prognostic marker of EC patients.

SCD catalyzed the production of MUFAs, mainly includes palmitoleic acid (16:1) and oleic acid (18:1), which subsequently were used to synthesize more complex lipids, like triglycerides and phospholipids [27, 80]. There are two types of SCD in human, SCD1 and SCD5, and the role of SCD1 is relatively definite [81]. A series of researches demonstrated SCD1 protected cancer cells from ferroptosis threatening, and inhibiting SCD1 effectively suppressed tumor growth and induced cell death [82–84], thus potentially beneficial to prevent cancer recurrence and metastasis. Interestingly, wild-type P53 was able to downregulate the expression of SCD1 by binding to its transcriptional promoter [85], suggesting that P53 mutant tumors may present aberrant lipid metabolism. A study reported that compared to secretory-phase and postmenopausal endometrium, SCD1 was significantly highly expressed in proliferative-phase, hyperplastic and malignant endometrium. More importantly, reduced SCD1 expression showed inhibitory effect on tumor growth in mice [86]. These findings reveal that SCD1 overexpression may contribute to maintaining cancer cell viability and promoting cancer progression, and SCD1 inhibition has significant killing effect on cancer cell, shedding light on treatment strategy establishment for EC.

Abnormally activated FA biosynthesis lays a solid foundation of cancer cell growth in EC, which can be effectively reversed by inhibiting FA production. The upregulation of FA *de novo* synthesis can be an unfavorable prognostic marker of EC patients, characterized by increased FASN and SCD expression, suggesting that enhanced FA synthesis may be involved in EC progression.

Increased cholesterol biosynthesis

Cholesterol biosynthesis is manipulated by HMGCR and SM, which are responsible for converting HMG-CoA to MVA (namely mevaleric acid pathway) and squalene to 2,3-epoxy squalene, respectively [87]. Recently, increased cholesterol synthesis has been considered to accelerate oncogenesis and tumor progression.

HMGCR was reported to be correlated with the risk of various cancers, and be involved in tumor growth and metastasis regulation [88–91]. FASN silencing could upregulate the expression of HMGCR by activating sterol regulatory element binding protein 2 (SREBP2), to enhance cholesterol production and cancer cell growth [92]. Besides, genetic alternation-induced HMGCR inactivation indicated reduced risk of ovarian cancer and breast cancer [93, 94], which lays a theoretic basis for the reuse of statins in anti-tumor treatment. Notably, analysis of transcriptomic sequencing data based on ovarian cancer, EC and cervix cancer showed that cholesterol related genes may contribute to tumoral resistance through cholesterol homeostasis and FA metabolism pathway [95]. These preliminary findings inspire researchers to explore the practicability of targeting HMGCR and predict tumoral response to anti-tumor therapy based on HMGCR expression status in EC.

SM, also called squalene cyclooxygenase (SQLE), was reported to promote tumor growth and progression in cancer [96–100]. Ma et al [101] has recently reported that significantly overexpressed SQLE was observed in EC patients by TCGA data analysis and IHC validation. Besides, SQLE drove the proliferation and metastasis of EC cell lines (Ishikawa and KLE) via upregulating PI3K/AKT signaling *in vitro*, which added the proofs of abnormal cholesterol metabolism to existing literatures in EC. Coates et al [102] initially revealed the upregulated truncation of SQLE could contribute to lipogenesis in EC. Hence, SQLE is commonly overexpressed to endogenously provide cholesterol for cancer cell and will become another therapeutic target in EC.

Acyl-CoA: cholesterol acyltransferase (ACAT), can transform free cholesterol into cholesterol ester, thus alleviating the cellular toxicity by overloaded free cholesterol [103]. There are two subtypes of ACAT in mammal animal as reported: ACAT1 (widely distributed) and ACAT2 (preferred in intestine and liver) [104]. ACAT was significantly correlated with recurrence-free

survival in cancer [105]. For EC, a study demonstrated the activity of ACAT in malignant endometrium was significantly greater than healthy secretory endometrium [106]. A study based on bioinformation analysis demonstrated that compared to normal tissue, seven cholesterol homeostasis related genes (like ACAT2) were significantly upregulated, and the constructed cholesterol homeostasis related genes signature could serve as a predictive tool of poor survival outcome for EC patients [107]. In all, increased expression of ACAT is able to facilitate the prognosis prediction of cancers, including EC, and reducing the expression of ACAT inhibits tumor growth. So, ACAT-mediated cholesterol esterification may play a critical role in tumor cell survival, which is worth further investigation in EC.

Previous researches have showed that the upregulated cholesterol biosynthesis pathway can boost malignant tumor survival and growth in EC. In addition, the key enzyme of cholesterol esterification, ACAT, is highly expressed in EC tissues, indicating the cholesterol metabolism related tumor protective mechanisms to some degree.

Abnormal lipid catabolism exerting diverse roles
Fat acid oxidation
Fat acid oxidation (FAO) is mainly conducted by mitochondrial β-oxidation and is able to drive the tumoral proliferation, metastasis and resistance, etc [108]. The initial program of FAO is that FAs are activated to acyl-CoA by long-chain acyl-CoA synthetase (ACSL). In the following, lipoylcarnitine is synthesized with acyl-CoA, catalyzed by carnitine palmitoyltransferase1 (CPT1) in outer mitochondrial membrane, and subsequently entry into the mitochondria, which is the speed-decisive step in FAO process [108] (Fig. 3). Quan et al [109] clarified that ACSL3 was upregulated by TGFβ1 via SREBP1 and stimulated ATP and NADPH generation by triggering FAO pathway, thus facilitating EMT and tumor spread. Tang et al [110] reported that high CPT1 expression greatly enhanced tumor proliferation, non-anchored growth and lesions formation. In EC, the abnormal expression or genetic changes of ACSL is linked to malignant biological characteristics and patients' prognosis. Zhou et al. [111] reported that ACSL1 overexpression upregulated
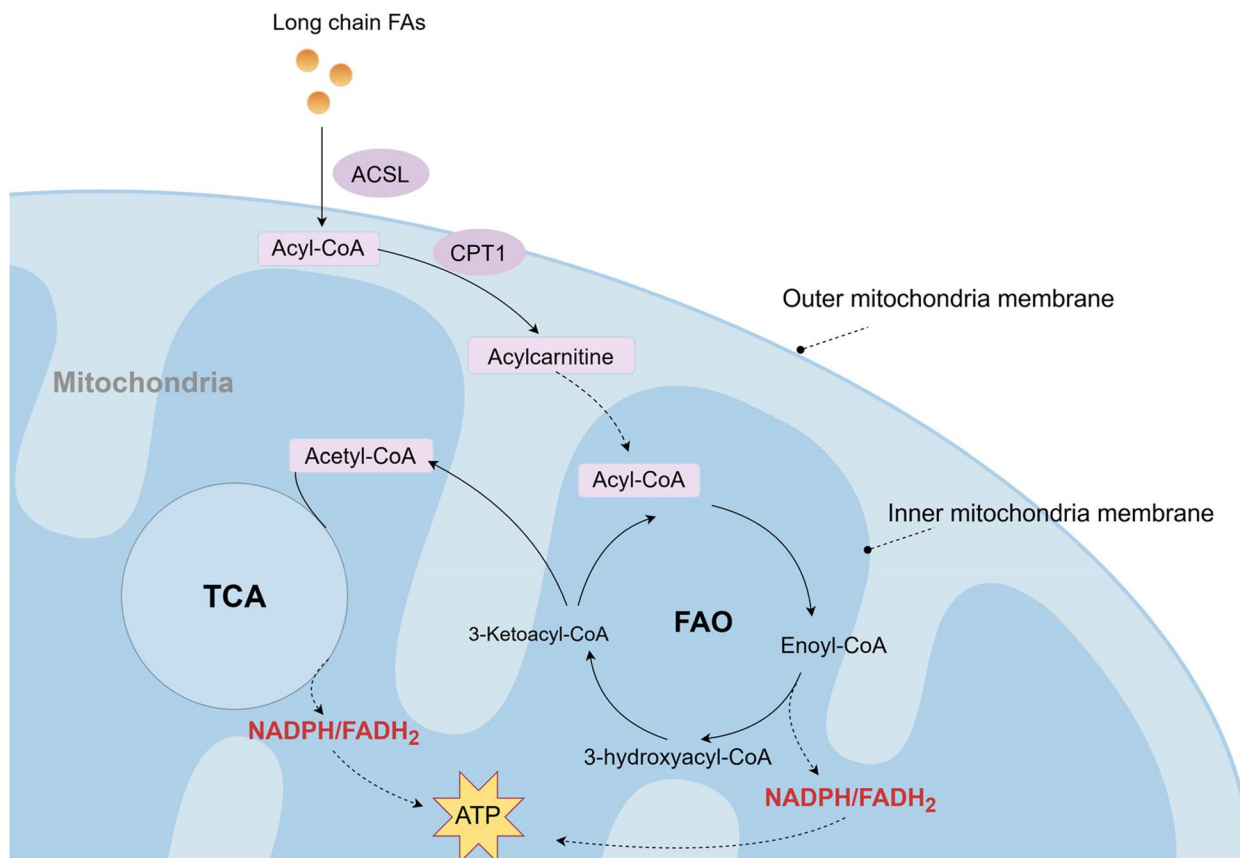

Fig. 3 The key enzymes and products of FAO in endometrial cancer. ACSL, long-chain acyl-CoA synthetase; CPT1, carnitine palmitoyltransferase1; FAO, fatty acid oxidation; TCA, tricarboxylic acid (By Figdraw)

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FAO process and energy provision by activating AMPK/CPT1C/ATP pathway, thus promoting cancer cell to proliferate and migrate, which was also predominantly associated with malignant advancement of EC. Yu et al [112] using UALCAN database found that compared to normal tissue, ACSL4 protein was relatively higher in EC lesions, consistent with the results from TIMER and GEPIA databases. According to HPA database, ACSL4 protein presented strongly positive in EC tissue. At the same time, ACSL4 genetic mutation suggested longer progression-free survival period of patients with EC while copy number amplification of ACSL4 predicted much worse outcome of the patients [112]. In short, FAO pathway upregulation may serve as a useful predictor for unfavorable prognosis of EC, and key enzymes like ACSL and CPT1 represent promising treatment targets in EC.

Cholesterol efflux

Cholesterol homeostasis is necessary for maintaining cancer cell survival and growth. Of note, over-accumulation of cholesterol is harmful to cancer cells. Cholesterol efflux has become an effective strategy to avoid lipid toxicity in cancer cell, because cholesterol is difficult to absolutely break down in human peripheral tissues. Four conventional cholesterol efflux pathways include: passive diffusion, SR-B1 promoting diffusion, ATP binding cassette subfamily A member 1 (ABCA1) mediating efflux to pre-β1 high-density lipoprotein (HDL) and ATP binding cassette subfamily G member 1 (ABCG1) mediating efflux to mature HDL [113, 114]. In EC, Antmen et al [115] discovered that ABCA1 was significantly higher in tumor tissues that control group. Interestingly, as the histodifferentiation of endometrial adenocarcinoma went worse (from grade 1 to grade 3), ABCA1 expression level presented a relatively decreasing trend, suggesting the tumor promoting role of increased cholesterol in cancer cell by reduced ABCA1 in endometrioid cancer. Besides, ABCA1 activation by NNMT1 can enhance cholesterol efflux and cellular membrane fluidity, thus stimulating EMT process of EC [116]. Additionally, higher HDL-cholesterol apparently increased the risk of non-endometrioid tumor [49], indicating cholesterol efflux may accelerate the development of EC with more malignant histological subtypes. Until now, ABCA1-mediated cholesterol efflux has been considered to be an adaptive approach of cancer cell to maintain cholesterol homeostasis and survival in EC. But whether some molecules of other cholesterol efflux ways will be involved in the intra-and extra-cellular cholesterol regulation and the underlying mechanisms should be further elucidated in EC.

Altered transcriptional regulation of lipid metabolism

SREBP

SREBP is a kind of transcription factors. Nuclear SREBP will activate lipid uptake and synthesis-related genes of lipid metabolism pathway by sterol regulating element (SRE). There have been three well-known SREBPs: SREBP1a, mainly regulating reactive genes in FA and cholesterol *de novo* synthesis processes; SREBP1c, affecting FA synthesis related genes and involving lipocyte differentiation, whose downstream enzymes includes ACC, FASN and SCD1;SREBP2, responsible for regulating cholesterol uptake and synthesis by influencing LDLR and HMGCR [24, 117–119].

SREBP1 and SREBP2 as well as downstream enzymes regulated by them were involved in lipid metabolism reprogramming and disease progression in cancer [120, 121]. Shafiee et al [122] reported SREBP1 was significantly elevated in EC tissues than in health tissues, positively associated with serum triglycerides. Li et al [123] found that compared to normal tissues, SREBP1 was significantly upregulated in poorly differentiated EC tissues and mainly located in nucleus, indicating its tumor-promoting effect in EC. Besides, SREBP1 target molecules (like FASN, SCD and ACLY) were overexpressed in AN3CA EC cell line, and the expression of these key enzymes were accordingly reduced by SREBP1 downregulation by shRNA. Subsequent experiments demonstrated SREBP1 knockdown hindered proliferation and growth, and showed tumor killing effects in EC. Qiu et al [124] analyzed the SREBP1 gene in EC lesions ($n=30$) and benign specimens ($n=6$) based on high throughput sequencing, with single nucleotides polymorphisms (rs2297508) as the target marker. Consequently, single nucleotides polymorphisms (rs2297508) and C alleles was detected in 40% of EC, significantly more frequent than control group and linked to the histological differentiation and involvement of myometrium. The above studies demonstrate that the upregulation and some specific genetic variations of SREBP1 define malignant characteristics of EC, so SREBP1 inhibition may facilitate tumor regression by reducing lipid provision (endogenous synthesis and exogeneous uptake).

Liver X receptor

Liver X receptor (LXR), a nuclear receptor super family member, includes LXRα and LXRβ. LXR can act as a transcriptional regulator of SREBP1c and maintain cholesterol homeostasis [118, 125]. For one thing, LXR is combined and activated by a variety of oxidized sterols, then binding to retinol X receptor to form a heterodimer, specifically enhancing SREBP1c transcription to increase FA synthesis [126, 127], further promoting

free cholesterol esterification to reduce extra toxicity from free cholesterol. For another, LXR activation could positively regulate ABCA1 expression to potentiate cholesterol efflux, and ubiquitously suppress LDLR by inducing Idol expression at transcription level, thus reducing cholesterol uptake [125, 128]. Otherwise, LXR activation could also induce the transcription of phospholipid remodeling enzyme (LPCAT3), preferentially driving the incorporation of unsaturated FAs into phospholipids to maintain the membrane homeostasis [129]. Fang et al [130] found by immunohistochemistry analysis that compared to normal and endometrial polyp tissues, LXRα was apparently overexpressed in endometrioid EC lesion and mainly distributed in cytoplasm of Ishikawa cell line. In addition, LXR impaired endometrial adenocarcinoma cell viability by inhibiting cyclin D1 and cyclin E expression. 27- hydroxycholesterol, a product of cholesterol metabolism, could be an endogenous activator of LXR and estrogen receptor [131]. Gibson et al [132] reported 27- hydroxycholesterol selectively activated estrogen receptor signaling to stimulate proliferation of Ishikawa and RL95-2 cells, which was reversed by external activation of LXR. Given that LXR has multiple effects on lipid metabolism regulation, systematic knowledge of LXR and of its upstream/downstream regulation mechanisms in EC should be established, to guide the exploration of effective therapeutic agents targeting LXR.

PPAR

PPAR belongs to nuclear hormone receptor super family and regulates lipid metabolism as a ligand-induced transcription factor [133, 134]. There are three subtypes of PPAR: PPARα, regulating FA transportation, esterification and oxidation processes; PPARβ/δ, mainly involving in FA oxidation; PPARγ, enhancing energy accumulation by affecting FA transportation, fat production and FA biosynthesis [133]. PPAR was reported to participate in diverse biological processes, such as tumor proliferation, vessels formation, invasion/metastasis, self-renewing, metabolism and immunology, etc [135].

Until now, related studies have demonstrated PPAR activation may exert anti-tumor effects in EC. A series of data supported PPARα and PPAR β/δ were expressed more strongly in EC tissues than non-malignant tissues, while the expression level of PPARγ was relatively decreased in EC [136–140]. But another study has reported that the expression of PPARα was lower in EC tissues than normal tissues recently [141]. Despite the distinct expression profiles of PPARα and PPARγ, their activation both inhibited tumor cell proliferation and angiogenesis in EC [140, 141]. Moreover, PPARγ activation attenuated proliferation, migration and invasion abilities of EC cells (especially EEC-1) and downregulated

the estrogen receptor expression in estrogen receptor-positive EEC-1 cell line [138]. Additionally, activated PPARβ/δ exerted anti-tumor effect by inhibiting AKT/GSK3β/β-catenin pathway [142]. Previous studies have revealed both PPAR activation and inhibition have shown anti-tumor potential, which broaden our perspectives of complicated lipid metabolism transcriptional regulation and will arouse researchers' interest to further investigate the underlying mechanisms and evaluate the effectiveness of targeting PPARs in EC. The key point is how to balance the status of PPARs to hinder the tumor progression of EC.

Targeting lipid metabolism as monotherapy in endometrial cancer

Growing studies have shown lipid metabolism alternations are associated with the occurrence, invasion, metastasis and recurrence of various cancers (including EC). Therefore, targeting key enzymes and related transcription factor of lipid metabolism pathway could be potential therapeutic strategy to inhibit cancer progression in EC (Fig. 4). Until now, a series of drugs targeting lipid metabolism pathway have been used as monotherapy to evaluate preclinical and clinical anti-tumor activity in EC.

FASN inhibitor

FASN is speed-limiting in FA synthesis pathway, and its overexpression will activate FA synthesis process, promoting EC invasion and migration. Due to this, inhibiting FA metabolism is a charming tumor interventional strategy and FASN inhibitors are increasingly developed in anti-tumor treatment. Orlistat, a robust FASN inhibitor, has been proved to reprogram oncological biology [143]. Wysham et al [144] assessed the anti-tumor activity of orlistat in ECC-1 and KLE cell lines and found orlistat at 500μM level could make the proliferative activity of cancer cells decrease by 61% and 57%, respectively. What's more, Western blot analysis indicated orlistat reduced the expression of core enzymes (like FASN, ACC and CPT1A) in lipid metabolism pathway, upregulated phosphorylated AMPK expression and downregulated phosphorylated AKT expression. Mycotoxin cerulenin is a covalently bound inactivator of FASN and C75 is a novel small molecular inhibitor of FASN. Menendez et al [79] reported that cerulenin and C75 treatment remarkably abrogated tamoxifen-activated estrogen response element-relied transcription and estradiol-induced upregulation of oncogenes (like ERα and HER2), thus probably preventing malignant transformation of endometrium and inhibiting the viability and proliferation of EC cells. Excitingly, a clinical trial first evaluated safety and
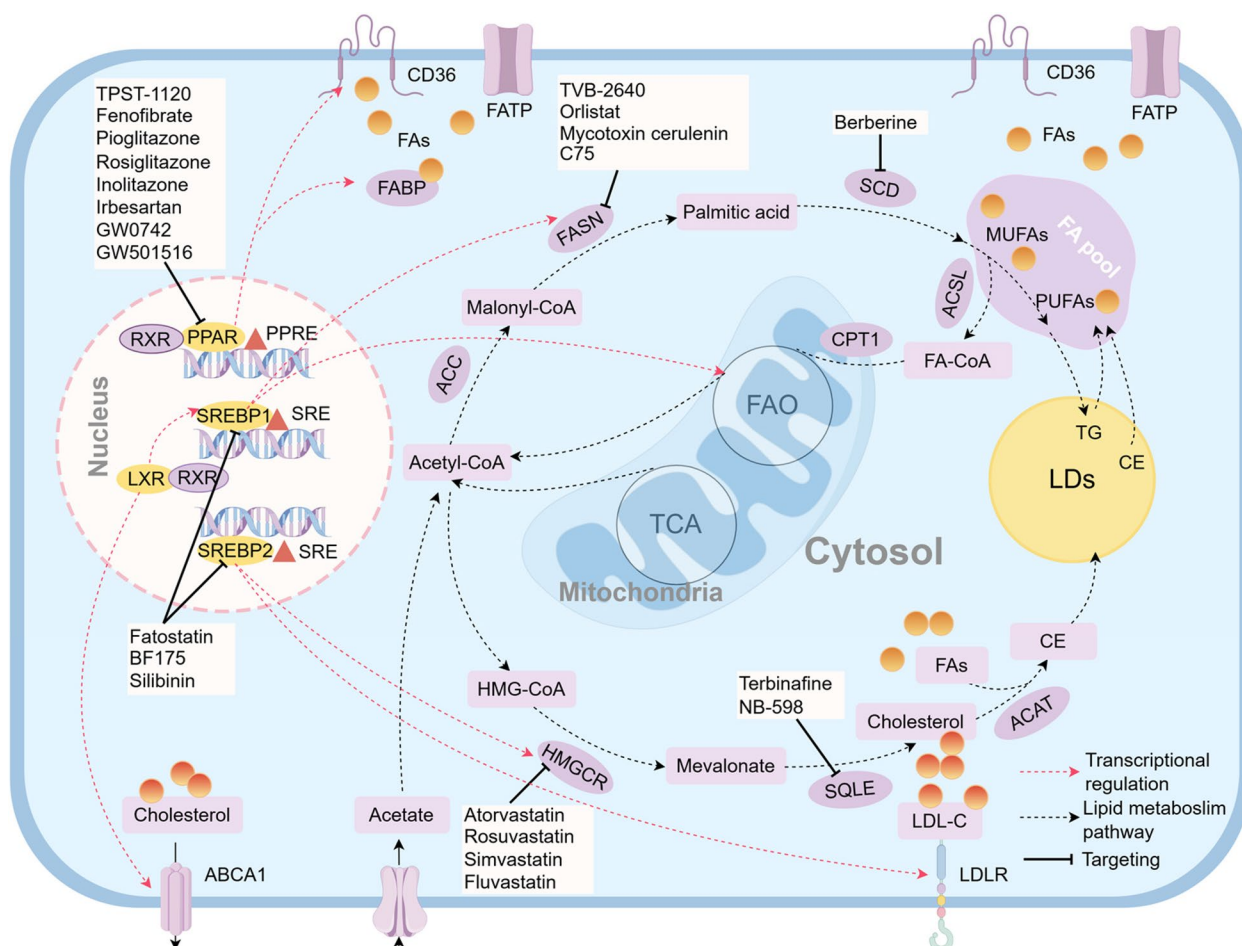
Fig. 4 Potential molecular targets and relevant agents of lipid metabolism in endometrial cancer. sterol regulatory element binding protein (SREBP) activates lipid uptake and synthesis-related genes of lipid metabolism pathway by sterol regulating element (SRE). SREBP2 is responsible for regulating cholesterol uptake and synthesis by influencing low-density lipoprotein receptor (LDLR) and 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR). Activated liver X receptor (LXR) binds to retinol X receptor (RXR) to form a heterodimer, specifically enhancing SREBP1c transcription to increase fatty acid (FA) synthesis and maintaining cholesterol homeostasis. LXR activation can also positively regulate ATP binding cassette subfamily A member 1 (ABCA1) expression to potentiate cholesterol efflux, and ubiquitously suppress LDLR. Peroxisome proliferation activates receptor (PPAR) regulates lipid metabolism by influencing FA uptake, FA synthesis and fatty acid oxidation (FAO). Notably, fatty acid synthase (FASN), stearic acid desaturase (SCD1), 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR), squalene cyclooxygenase (SQLE), SREBP and PPAR are potential therapeutic targets of aberrant lipid metabolism in endometrial cancer (By Figdraw)

pharmacology of FASN inhibitor TVB-2640 (denifanstat) alone ($n=76$) or combined with paclitaxel ($n=60$) in advanced solid tumors (EC included). TVB-2460 monotherapy was able to accomplish a disease control rate of 42%. TVB-2640 combined with paclitaxel would reach 70% disease control rate and 12% partial response rate, with manageable drug safety [145]. Preclinical studies reveal that FASN inhibitors have initial anti-tumor activity and more clinical trials are in need to evaluate the feasibility of applying FASN inhibitors in EC patients with lipid metabolic disorder.

SCD1 inhibitor
SCD1 is responsible for the generation of unsaturated FAs, involving cancer ferroptosis resistance and metastasis, which has been considered as a potent target for cancer therapy [84, 146]. SCD1 knockdown or inhibited by A939572 damaged the tumor cell growth, promoted apoptotic program *in vitro* and abrogated the capability of metastatic lesions formation of EC AN3CA cell line *in vivo* [86].

HMGCR inhibitor

HMGCR, key enzyme of cholesterol biosynthesis, is highly expressed in cancer, to satisfy the extra need of cholesterol for tumor growth. Statins are able to regulate lipids level by inhibiting HMGCR and have been widely used in cardiovascular diseases management. More importantly, statins were reported to reduce the risk of tumorigenesis and improve prognosis benefits in cancers [147]. Hence, the repurposing of statins in anti-tumor field has become a hot topic [148]. Simvastatin is first-generation HMGCR inhibitor. Schointuch et al [149] found simvastatin treatment significantly inhibited the proliferation, invasion and migration ability of ECC-1 and Ishikawa cell lines as well as primary cancer cells derived from EC patients. Zhou et al. revealed [150] that simvastatin could block cancer cell proliferation and invasion by downregulating the RAS/MAPK signaling and induce reactive oxygen species and ferroptosis. Moreover, simvastatin plus metformin showed synergistic anti-tumor effects in RL95-2, HEC-1B and Ishikawa EC cell lines, possibly mediated by mTOR signaling and apoptosis [151]. Fluvastatin is the first completely synthesized second-generation HMGCR inhibitor. Cai et al [152]reported that fluvastatin impaired aggressive characteristics of EC cells and induced cell death. It should be emphasized that a clinical trial (NCT0276736) has accomplished the preliminary assessment of anti-proliferation activity of atorvastatin in EC.

SQLE inhibitor

SQLE is another rate-limiting enzyme for cholesterol biosynthesis. SQLE inhibitor like terbinafine and NB-598 effectively promoted the apoptosis and inactivated MAPK and PI3K/AKT pathway [153]. SQLE knockdown by shRNA or chemical inhibition by terbinafine could repress the P53-deficiency induced tumorigenesis and growth [154]. Du et al [155] proposed that SQLE was a promising therapeutic target in P53 mutant colorectal cancer, enlightening the novel treatment strategy of P53 mutant tumors. Silencing or pharmacological inhibition by terbinafine obviously reduced tumor growth of EC, indicating the therapeutic potential of SQLE inhibitor [101].

SREBP inhibitor

SREBP transcriptionally regulates lipid biosynthesis in various malignant tumors, and inhibiting SREBP may become a potent anti-tumor strategy. Fatostatin is an inhibitory agent of SREBP. Gao et al [156] revealed that fatostatin treatment could suppress the viability, clone formation and aggressiveness of EC cells, and exerted tumor killing effects by initiating cancer cell apoptosis, where SREBP1 and its downstream lipid synthases were noticeably downregulated with decreased intracellular free FAs and cholesterol. Similarly, Yao et al [157] also discovered fatostatin resulted in tumor regression by targeting lipid metabolism by *in vitro* and *in vivo* experiments. Research results in xenograft model have demonstrated fatostatin suppressed tumor growth and expansion, simultaneously disturbing tumor cell cycle and promoting cell death in EC. BF175, a new SREBP inhibitor, has shown lipid-lowering effects. Wang et al [158] initially reported BF175 dramatically hindered cell proliferation and migration of AN3CA cells by triggering autophagy and mitochondrial pathway associated apoptosis. In addition, BF175 also effectively downregulated SREBP and its downstream genes, to reduce FAs and cholesterol production. Furthermore, novel anti-tumor drug silibinin was considered to block lipid synthesis by inactivating STAT3 and SREBP signaling, causing damaged cell proliferation and activated apoptosis in EC [159]. Though *in vitro* and *in vivo* experiments suggest that SREBP inhibitor contribute to tumor inhibition, its safety and activity should be determined in more basic and clinical studies.

PPAR modulator

PPAR acted as a transcriptional regulator of lipid metabolism, involved in a variety of oncological biological processes, including lipids transportation, synthesis and catabolism, etc. PPAR signaling also plays an important role in tumor immune response. Interestingly, PPARs have shown bilateral functions in cancer development. PPAR modulators (agonist and antagonist) were both reported to have great cancer management potential [133]. Fibrates can serve as PPARα agonist. Fenofibrate effectively improved the sensitivity of breast cancer, prostate cancer and non-small cell lung cancer to chemotherapy or targeted therapy [160–162]. In EC, fenofibrate was able to suppress cancer cell expansion and stimulate apoptosis probably by inhibiting PPAR regulating FA metabolism pathway [163, 164]. Irbesartan, as a PPAR agonist, can also inhibit the proliferation of EC HEC-1 A and Ishikawa cell lines, by simultaneously inactivating the SREBP1 and activating the tumor suppressing genes [141]. Classical PPARγ agonists are known as isthiazolidinediones, containing troglitazone, rosiglitazone, pioglitazone, ciglitazone and inolitazone/efatutazone, etc. Kumari et al [165] first investigated the anti-tumor efficacy of pioglitazone in EC mouse model ($n = 50$) and found that compared to standard paclitaxel treatment, pioglitazone inhibited tumor lesions formation and growth in a dose dependent manner. Furthermore,

GW0742 and GW501516 were two highly selective PPARβ/δ activators, able to activate PPAR signaling pathway, leading to the inhibition of tumoral proliferative capacity and apoptosis in EC [142]. Thus, the anti-tumor effect on part of PPAR modulators (mainly agonists), has been preliminarily determined in EC, but the anti-tumor efficacy of some PPAR inhibitors should be highlighted in future studies.

Collectively, targeting lipid metabolism pathway and related transcriptional regulation factors is a promising anti-tumor therapy in malignant tumors, and relevant agents has entered clinical trials (Table 1). The expansion of clinical trials in pan-cancer has encouraged the basic and clinical exploration of lipid metabolism-targeted therapies in EC (Table 2). Therefore, we could reasonably predict that targeting lipid metabolism will become spotlight of EC research in the approaching future, to prevent the development of EC and to improve the prognosis of EC patients, particularly in women with obesity or lipid metabolism disturbance.

Targeting lipid metabolism in combinational therapy of endometrial cancer

Given that solely targeting lipid metabolism pathway demonstrates promising therapeutic potential in EC management, its combination with immunotherapy is increasingly in development. Among lipid metabolism pathway targeted drugs, PPAR modulators have been mostly reported to improve the anti-tumor efficacy of immunotherapy. Interestingly, in diet-induced obese female mice, GW9662 combined with anti-PD-L1 immunotherapy showed anti-tumor activity. A clinical study (NCT04114136) has been designed to explore whether PPARγ antagonist (rosiglitazone) can remodel tumor immune microenvironment to potentiate tumor killing effects of T cells and improve the tumoral sensitivity to anti-PD-1 treatment in solid tumors. Also, the safety and tolerance of rosiglitazone combined with nivolumab/pembrolizumab are closely monitored. In addition, NCT03829436 is a phase 1 clinical trial, aiming to determine the drug toxicity and maximum tolerant dosage of

Table 1 Clinical trials of targeting lipid metabolism in malignancies (ClinicalTrials.gov)

Drug	Target	Effect	Malignancy	Phase	Patient	NCT Number
TVB-2640 (Denifanstat)	FASN	Inhibitor	KRAS-mutant non-small cell lung carcinoma	Phase 2	34	NCT03808558
TVB-2640 (Denifanstat)	FASN	Inhibitor	HER2-positive metastatic breast cancer	Phase 2	19	NCT03179904
TVB-2640 (Denifanstat)	FASN	Inhibitor	Recurrent high-grade astrocytoma	Phase 2	25	NCT03032484
TVB-2640 (Denifanstat)	FASN	Inhibitor	Metastatic castration-resistant prostate cancer	Phase 1	30	NCT05743621
TVB-2640 (Denifanstat)	FASN	Inhibitor	Colon cancer	Phase 1	48	NCT02980029
TVB-2640 (Denifanstat)	FASN	Inhibitor	Solid malignant tumor	Phase 1	180	NCT02223247
Berberine	SCD1	Inhibitor	EGFR-mutant lung adenocarcinoma	Phase 2	50	NCT03486496
Atorvastatin	HMGCR	Inhibitor	Hepatocellular carcinoma	Phase 4	240	NCT03024684
Atorvastatin	HMGCR	Inhibitor	Metastatic/recurrent prostate cancer	Phase 3	400	NCT04026230
Atorvastatin	HMGCR	Inhibitor	Breast cancer	Phase 3	314	NCT03971019
Atorvastatin	HMGCR	Inhibitor	HER2 negative breast cancer	Phase 2 Phase 3	60	NCT05103644
Atorvastatin	HMGCR	Inhibitor	High-risk stage IIA melanoma	Phase 2	150	NCT06157099
Atorvastatin	HMGCR	Inhibitor	Locally advanced prostate cancer	Phase 2	364	NCT01759836
Atorvastatin	HMGCR	Inhibitor	p53-mutant and wild-type malignancies	Phase 1	50	NCT03560882
Simvastatin	HMGCR	Inhibitor	Breast cancer	Phase 3	314	NCT03971019
Rosuvastatin	HMGCR	Inhibitor	Metastatic prostate cancer	Phase 4	70	NCT04776889
Rosuvastatin	HMGCR	Inhibitor	Rectal cancer	Phase 2	45	NCT02569645
Rosuvastatin	HMGCR	Inhibitor	Solid tumor	Phase 1	19	NCT04428086
Rosuvastatin	HMGCR	Inhibitor	Squamous cell carcinoma and non-small cell lung cancer	Phase 1	24	NCT00966472
Silibinin	SREBP	Inhibitor	EGFR-mutant lung adenocarcinoma	Phase 2	42	NCT02146118
Silibinin	SREBP	Inhibitor	Non-small cell lung cancer and breast cancer	Not applicable	70	NCT05689619
TPST-1120	PPAR	Antagonist	Advanced liver cancer	Phase 1 Phase 2	400	NCT04524871
TPST-1120	PPAR	Antagonist	Advanced cancer	Phase 1	138	NCT03829436
Inolitazone (Efatutazone)	PPAR	Agonist	Myxoid liposarcoma	Phase 2	15	NCT02249949
Inolitazone (Efatutazone)	PPAR	Agonist	Advanced anaplastic thyroid cancer	Phase 2	19	NCT02152137
Inolitazone (Efatutazone)	PPAR	Agonist	Colorectal cancer	Phase 2	84	NCT00986440
Pioglitazone	PPAR	Agonist	Lung cancer	Phase 2	92	NCT00780234
Pioglitazone	PPAR	Agonist	Pancreatic cancer	Phase 2	14	NCT01838317
Rosiglitazone	PPAR	Agonist	Liposarcoma	Phase 2	32	NCT00004180

Table 2 Preclinical and clinical studies of targeting lipid metabolism in endometrial cancer

Drug	Target	Effect	Objective	Study type	Reference
TVB 2640 (Denifanstat)	FASN	Inhibitor	Refractory metastatic or advanced solid malignant tumors (including endometrial cancer)	Clinical (Phase 1)	[145]
Orlistat	FASN	Inhibitor	Endometrial cancer ECC-1 and KLE cell lines	Basic	[144]
Mycotoxin cerulenin	FASN	Inhibitor	Endometrial cancer Ishikawa cell line	Basic	[79]
C75	FASN	Inhibitor	Endometrial cancer Ishikawa cell line	Basic	[79]
A939572	SCD1	Inhibitor	Endometrial cancer EEC-1, HEC-1 A, RL95-2, AN3CA, KLE, SPEC-2 cell lines	Basic	[86]
Atorvastatin	HMGCR	Inhibitor	Endometrial cancer patients	Clinical (Phase 2)	NCT05675787
Atorvastatin	HMGCR	Inhibitor	Endometrial cancer patients	Clinical (Phase 1)	NCT02767362
Rosuvastatin	HMGCR	Inhibitor	Endometrial cancer patients	Clinical (Phase 2)	NCT04491643
Simvastatin	HMGCR	Inhibitor	Endometrial cancer ECC-1 and Ishikawa cell lines, as well as primary cancer cells from patients	Basic	[149]
Simvastatin	HMGCR	Inhibitor	Endometrial cancer Ishikawa cell line	Basic	[150]
Simvastatin	HMGCR	Inhibitor	Endometrial cancer RL95-2, HEC-1 B and Ishikawa cell lines	Basic	[151]
Fluvastatin	HMGCR	Inhibitor	Endometrial cancer RL95-2 and KLE cell lines	Basic	[152]
Terbinafine	SQLE	Inhibitor	Endometrial cancer Ishikawa and KLE cell lines, and nude mice	Basic	[101]
Fatostatin	SREBP	Inhibitor	Endometrial cancer Ishikawa and HEC-1 A cell lines	Basic	[156]
Fatostatin	SREBP	Inhibitor	Endometrial cancer xenograft model	Basic	[157]
BF175	SREBP	Inhibitor	Endometrial cancer AN3CA cell lines	Basic	[158]
Silibinin	SREBP	Inhibitor	Endometrial cancer Ishikawa and RL95-2 cell lines	Basic	[159]
Fenofibrate	PPAR	Agonist	Endometrial cancer Ishikawa cell line	Basic	[164]
Irbesartan	PPAR	Agonist	Endometrial cancer HEC-1 A and Ishikawa cell lines	Basic	[141]
Pioglitazone	PPAR	Agonist	Endometrial cancer mice model	Basic	[165]
GW0742	PPAR	Agonist	Endometrial cancer Ishikawa, RL95-2 and Sawano cell lines	Basic	[142]
GW501516	PPAR	Agonist	Endometrial cancer Ishikawa, RL95-2 and Sawano cell lines	Basic	[142]

PPARα antagonist (TSPT-1120) alone or combined with nivolumab (PD-L1 inhibitor) in advanced solid tumor. NCT04524871 is designed to evaluate clinical efficacy of different combinations of immunotherapy in advanced liver cancer, including atezolizumab (PD-1 inhibitor), bevacizumab and TSPT-1120.

Simultaneously, progesterone is applied in systematic management of EC, but tumor resistance to progesterone has severely decreased its clinical efficacy. Inspiringly, the strategy of targeting lipid metabolism pathway combined with progesterone is undergoing preliminary clinical investigation. A phase 2 clinical study (NCT05675787) is recruiting patients, in order to assess the efficacy of MPA plus atorvastatin in young patients with early-stage EC. Another phase 2 clinical trial (NCT04491643) is to investigate the anti-tumor effects of MA in combination with rosuvastatin in young, stage I EC patients. Similarly, Progesterone regimen and several statins are applied in patients with early-stage EC (NCT06102863).

Therefore, these active clinical researches strongly support that targeting lipid metabolism pathway sensitizing immunotherapy has become a potentially promising anti-tumor strategy in advanced solid tumor, and particularly in EC (Table 3). On one hand, anti-PD-1/ PD-L1 immunotherapy has made breakthrough in EC chemical intervention, so it's necessary to further investigate whether lipid metabolism targeted therapy added to immunotherapy can rescue more patients with EC. On the other hand, the therapeutic efficacy of lipid metabolism pathway targeted drugs (especially statins) plus progesterone is required to elucidate its potential as a conservative treatment for women at high risk of EC (such as obesity, metabolic syndrome and dyslipidemia) and to improve the survival of EC patients.

Conclusion

The increasing incidence and morality of EC can be largely attributed to metabolic disorders like obesity and hyperlipidemia. Lipid metabolism reprogramming is initiated by genetic alternations especially P53 mutation, which is remarkably associated with the worst prognosis of EC patients. In general, the activated endogenous lipogenesis (FA and cholesterol biosynthesis) and FAO process play a pivotal role in inducing tumor initiation, proliferation, invasion, metastasis and stemness, as well as tumor microenvironment remodeling and therapeutic resistance in EC. Besides, various signaling pathways are rewired by aberrant lipid metabolism to elicit

Table 3 Clinical trials of targeting lipid metabolism pathway in combinational therapy of cancers (ClinicalTrials.gov)

Regimen	Drug	Malignancy	Patient	Phase	NCT Number
Hormone therapy + HMGCR inhibitor	Progesterone + Atorvastatin/ Rosuvastatin/ Pivastatin	Endometrial carcinoma stage I	38	Phase 2	NCT06102863
Hormone therapy + HMGCR inhibitor	Medroxyprogesterone acetate + Atorvastatin	Endometrial carcinoma stage I	82	Phase 2	NCT05675787
Hormone therapy + HMGCR inhibitor	Megestrol Acetate + Rosuvastatin	Endometrial carcinoma stage I	48	Phase 2	NCT04491643
PD-1 inhibitor + PPAR agonist	Nivolumab/ Pembrolizumab + Rosiglitazone	Solid tumor malignancies	72	Phase 2	NCT04114136
PD-1 inhibitor + PPAR antagonist	Nivolumab + TPST-1120	Advanced cancers	38	Phase 1	NCT03829436
PD-L1 inhibitor + PPAR antagonist	Atezolizumab + TPST-1120	Advanced liver cancers	400	Phase 1/2	NCT04524871

tumor-promoting functions (Fig. 5). The alternations of some key enzymes (especially FASN, SCD1, HMGCR and SQLE) and transcriptional factors (SREBP, LXR and PPAR) define the lipid metabolism dysregulation in tumorigenesis and progression of EC, which has become the excellent candidate targets for treatment exploration. To date, drugs targeting lipid metabolism related

pathway have shown preliminary anti-tumor activity in EC. Importantly, sensitizing hormonal therapy by targeting lipid metabolism pathway is undergoing assessment in early phase clinical trials in EC.

Although the close association between lipid metabolism reprogramming and EC has been established, there is still a long way to go to dissect the roles of lipid
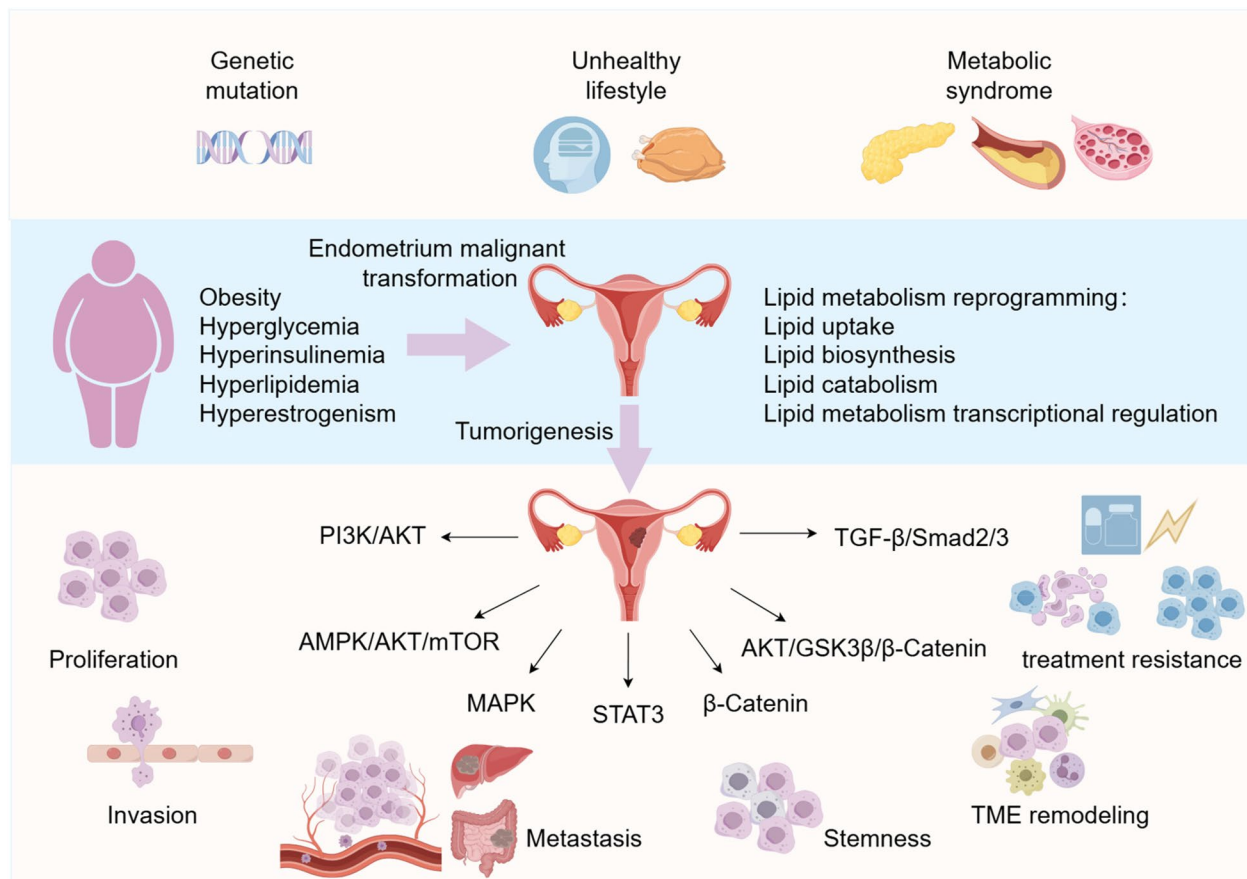

Fig. 5 The landscape of aberrant lipid metabolism and potential mechanisms in tumorigenesis and cancer progression of endometrial cancer (By Figdraw)

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metabolism pathways. Firstly, to what degree the lipid uptake and its core driving molecules can be involved in the initiation and progression of EC remains contradictory. Next, the transcriptional factor, PPARs, show diverse expression profiles, which leads to the exploration of their precision targeting strategy challenging. What's more, hormone in combination with lipid metabolism targeted treatment has been applied in clinical trials, but the definite efficacy of preventing endometrial malignant transformation and inhibiting cancer progression is awaiting robust evidence. More importantly, sensitizing immunotherapy by rewiring the lipid metabolism is a promising direction for advanced/metastatic EC management due to the encouragement of several clinical trials in other malignancies, and the theoretical basis and clinical benefits should be further determined.

In conclusion, lipid metabolism reprogramming has become a hallmark of EC, which not only participates in the occurrence and advancement of tumor, but also has proposed as an interventional strategy. As studies increasingly accumulate, it's expected to depict a comprehensive landscape of lipid metabolism in EC. In the future, researchers should focus on clarifying the pathological roles of different branches of lipid metabolism pathway and their interaction with the tumor microenvironment, and developing novel targetable molecules to decrease the tumor burden and hinder the cancer progression.

Abbreviations
ABCA1	ATP binding cassette subfamily A member 1
ABCG1	ATP binding cassette subfamily G member 1
ACAT	Acyl-CoA: cholesterol acyltransferase
ACC	Acetyl-CoA carboxylase
ACLY	ATP-citrate lyase
ACSS2	Acetyl-CoA synthetase 2
ACSL	Long-chain acyl-CoA synthetase
CPT1	Carnitine palmitoyltransferase1
EC	Endometrial cancer
EMT	Epithelial-mesenchymal transition
FA	Fatty acid
FAO	Fatty acid oxidation
FASN	Fatty acid synthase
FATP	Fatty acid transport protein
HDL	High-density lipoprotein
HMGCR	3-hydroxy-3-methyl glutaryl coenzyme A reductase
LDLR	Low-density lipoprotein receptor
LDL-C	Low-density lipoprotein-cholesterol
LXR	Liver X receptor
MUFA	Monounsaturated fatty acid
PPAR	Peroxisome proliferator-activated receptor
PUFA	Polyunsaturated fatty acid
SCD1	Stearic acid desaturase 1
SM	Squalene monooxygenase
SQLE	Squalene cyclooxygenase
SRE	Sterol regulating element
SREBP	Sterol regulatory element binding protein

Declarations

Competing interests
The authors declare no competing interests.

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