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Review Article

Metabolic reprogramming in endometriosis: mechanisms and therapeutic prospects

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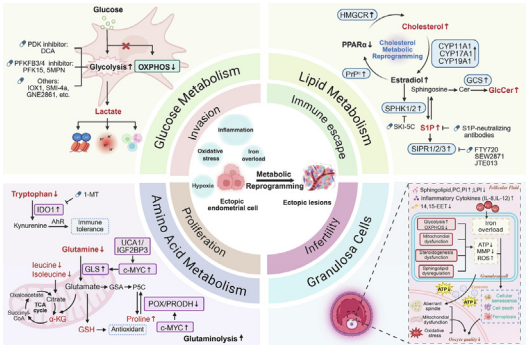
HIGHLIGHTS

- Major mechanisms of metabolic reprogramming in endometriosis (EMS) were elucidated.
- Lactate promotes EMS via lactylation, intercellular communication, and immune remodeling.
- Metabolic reprogramming in granulosa cells leads to poor oocyte quality and infertility.
- An integrated "metabolic crosstalk" network sustains ectopic lesion survival and progression.
- Targeting metabolic vulnerabilities for precision therapy: strategies and challenges.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Endometriosis (EMS) is an estrogen-dependent chronic inflammatory disorder for which metabolic reprogramming has emerged as a central pathological feature. Driven by genetic, epigenetic, and microenvironmental stressors, ectopic endometrial cells undergo extensive metabolic remodeling integrating energy production, redox homeostasis, and biosynthetic demands. These adaptations not only sustain cell survival under hypoxia and inflammation, but reshape epigenetic marks and the immune microenvironment, promoting lesion progression and impairing reproductive function.

Aim of review: This review systematically outlines the molecular mechanisms of metabolic reprogramming in EMS, examines its impact on lesion development and fertility, and evaluates the potential of targeting metabolic pathways for precision therapy.

Key scientific concepts: Ectopic endometrial cells display a phenotype with enhanced aerobic glycolysis, dysregulated fatty acid oxidation and phospholipid synthesis, and abnormal amino acid metabolism. These alterations support lesion survival and proliferation through epigenetic and immune modulation. Granulosa cell metabolic reprogramming—characterized by excessive glycolysis, mitochondrial dysfunction, lipid accumulation, and iron overload—disrupts oocyte energy and redox balance, reducing oocyte quality, and contributing to EMS-associated infertility. Preclinical studies suggest that targeting glucose,

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lipid, and amino acid pathways could mitigate disease phenotypes; however, metabolic plasticity, overlap with physiological metabolism, and safety concerns limit clinical translation. These challenges highlight the need for combinatorial interventions, precise delivery, and optimized therapeutic strategies to improve patient outcomes.

Contents

Introduction

Endometriosis (EMS) is an estrogen-dependent chronic inflammatory disease affecting approximately 10% of women of reproductive age worldwide. Among patients with EMS, 25–30% experience infertility. The prevalence of EMS in women with infertility is as high as 50% [1,2]. Characterized by the ectopic growth of active endometrial tissue in pelvic and extra-pelvic sites, EMS causes chronic inflammation, pain, and infertility, markedly reducing quality of life. Despite being histologically benign, it exhibits tumor-like behaviors such as invasion, angiogenesis, immune evasion, and recurrence, implying shared molecular mechanisms with malignancies.

In the past few years, high-throughput omics technologies have revealed that endometriotic lesions are not homogeneous inflammatory masses, but consist of cellular subpopulations with highly heterogeneous metabolic phenotypes [3–5]. In order to adapt to the microenvironment of hypoxia, inflammation, oxidative stress, and iron overload, these cells actively reprogram glucose, lipid, and amino acid metabolism to satisfy energy and biosynthetic demands. This echoes the ‘‘aerobic glycolysis” phenomenon first described by Otto Warburg in 1924 [6]. Its core principle lies in supporting rapid cell proliferation through swift energy supply and provision of biosynthetic precursors [7]. In EMS, such metabolic conversion fuels lesion growth and disrupts the ovarian follicular niche, compromising oocyte quality and contributing to infertility.

Although metabolic reprogramming is increasingly recognized as a hallmark of EMS, the underlying mechanisms driving disease progression and the complex interplay between distinct metabolic pathways remain poorly understood. This review therefore aims to characterize the molecular features and regulatory networks of glucose, lipid, and amino acid metabolic reprogramming in EMS and analyze their interactions with key pathological processes such as immune dysregulation, angiogenesis, and epithelial–mesenchymal transition (EMT), with a focus on the contribution of metabolic abnormalities to EMS-associated infertility. This work also explores precision therapeutic strategies based on metabolic

Table 1
Dysregulated metabolites in endometriosis.

Metabolism Type	Metabolite	Change	Sample Source	Stage(s)	Analytical Method	Ref.
Glycolysis	Lactate	↑	Serum; FF	Not specified	1H NMR	[60,82]
	Glucose	↓	Serum; FF	Not specified	1H NMR	[60,82]
	Pyruvate	↑	Serum; FF	Not specified	1H NMR	[60,82]
	Citrate	↑	Serum	Not specified	1H NMR	[82]
		↓	FF	Not specified	1H NMR	[60]
	β-D-Glucose-6-phosphate	↑	FF	III–IV	LC-MS/MS	[63]
Lipid Metabolism	Sphingomyelin	↑	Plasma; FF	III–IV	ESI-MS/MS	[13,159]
		↓	EF	Not specified	UPLC-MS	[59]
	Phosphatidylcholine (PC)	↑	FF	III–IV	ESI-MS	[159]
	Phosphatidylinositol (PI)	↑	FF	Not specified	LC-MS/MS	[134]
	Lysophosphatidylinositol	↓	FF	Not specified	LC-MS/MS	[134]
	Lysophosphatidic acid	↑	FF	Not specified	LC-MS/MS	[134]
	Ceramide	↑	Menstrual blood	All stages	RP-HPLC-MS	[160]
		↓	EF	Not specified	UPLC-MS	[59]
	Triglycerides	↑	Venous blood; Serum; Menstrual blood	III–IV; III–IV; All stages	Enzymatic method; MS; RP-HPLC-MS	[53,160,161]
		↓	EF	Not specified	UPLC-MS	[59]
	Total cholesterol	↑	Venous blood	III–IV	Enzymatic method	[53]
	Non-HDL cholesterol	↑	Venous blood	III–IV	Enzymatic method	[53]
	HDL	↑	Venous blood	III–IV	Enzymatic method	[53]
	LDL	↑	Venous blood	III–IV	Enzymatic method	[53]
	Acylcarnitines	↓	FF	III–IV	LC-MS/MS	[63]
		↑	EF	Not specified	UPLC-MS	[59]
Amino Acid Metabolism	Arginine	↓	Serum	Not specified	1H NMR	[82]
	Tryptophan	↓	Serum	IV	1H NMR	[83]
	Alanine	↓	FF; Endometrial tissue	Not specified; All stages	1H NMR	[60,162]
	Lysine	↑	Serum; Endometrial tissue	III–IV; I–II	LC-MS/MS; UHPLC-ESI-HRMS	[163,164]
		↓	Endometrial tissue	All stages	1H NMR	[162]
	Isoleucine	↓	Serum	Not specified	1H NMR	[61]
	Leucine	↓	Serum; Endometrial tissue	Not specified; All stages	1H NMR	[61,162]
		↑	Endometrial tissue	I–II	UHPLC-ESI-HRMS	[164]
	Valine	↓	Serum; FF	Not specified	1H NMR	[61,165]
	Proline	↓	Endometrial tissue	All stages	1H NMR	[162]
	Tyrosine	↓	Serum	Not specified	1H NMR	[61]
	Glutamate	↓	Serum	Not specified	1H NMR	[61]
	Glutamine	↑	FF	III–IV	LC-MS/MS	[63]
		↓	Serum	Not specified	1H NMR	[61]
	Histidine	↓	Serum	Not specified	1H NMR	[61]
	Threonine	↓	Serum	Not specified	1H NMR	[61]

Abbreviations: FF, follicular fluid; NMR, nuclear magnetic resonance; LC-MS/MS, liquid chromatography-tandem mass spectrometry; ESI-MS/MS, electrospray ionization tandem mass spectrometry; EF, endometrial fluid; UPLC-MS, ultra-performance liquid chromatography-mass spectrometry; ESI-MS, electrospray ionization mass spectrometry; MS, mass spectrometry; RP-HPLC-MS, reverse-phase high-performance liquid chromatography-mass spectrometry; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UHPLC-ESI-HRMS, ultra-high performance liquid chromatography electrospray ionization high-resolution mass spectrometry.

vulnerabilities, offering new perspectives and potential intervention avenues to overcome the limitations of traditional hormonal therapies.

Metabolic reprogramming in EMS

EMS is highly heterogeneous: its cellular and structural diversity combine to shape a complex metabolic phenotype. Ectopic lesions exhibit hallmarks of metabolic reprogramming, including enhanced aerobic glycolysis with suppressed oxidative phosphorylation [8,9], dysregulated fatty acid oxidation and phospholipid synthesis [10–13], and altered amino acid metabolism [14]. These alterations not only provide energy and biosynthetic precursors for rapidly proliferating ectopic endometrial cells but also remodel the microenvironment, regulate immune responses, and induce epigenetic modifications. Collectively, they establish a supportive "metabolic niche" which sustains lesion growth, invasion, and immune escape. The following sections will discuss the features and molecular mechanisms of metabolic reprogramming in EMS, focusing on glucose, lipid, and amino acid metabolism, to lay the groundwork for targeted metabolic therapies. The key metabolic dysregulations have been systematically summarized (see Table 1). Notably, the patterns of metabolite dysregulation presented in Table 1 are not uniform. Metabolites such as triglycerides, acylcarnitines, and lysine show contradictory trends across different studies (e.g., serum vs. tissue). These discrepancies likely arise from differences between systemic and local metabolism, stage specific metabolic demands, and technical variability, and also suggest the potential for metabolic subtyping in this disease.

Glucose metabolic reprogramming

In EMS, ectopic endometrial cells exhibit a pronounced glycolytic phenotype characterized by increased glucose uptake, activation of glycolytic enzymes, and lactate accumulation. This metabolic shift not only remodels energy supply but also drives disease progression through multiple mechanisms (Fig. 1).

Regulation of glycolytic enzymes

Key glycolytic enzymes serve as central executors of metabolic rewiring. Ectopic endometrial cells exhibit significantly enhanced glycolysis, compensating for the lower ATP yield of glycolysis rela-

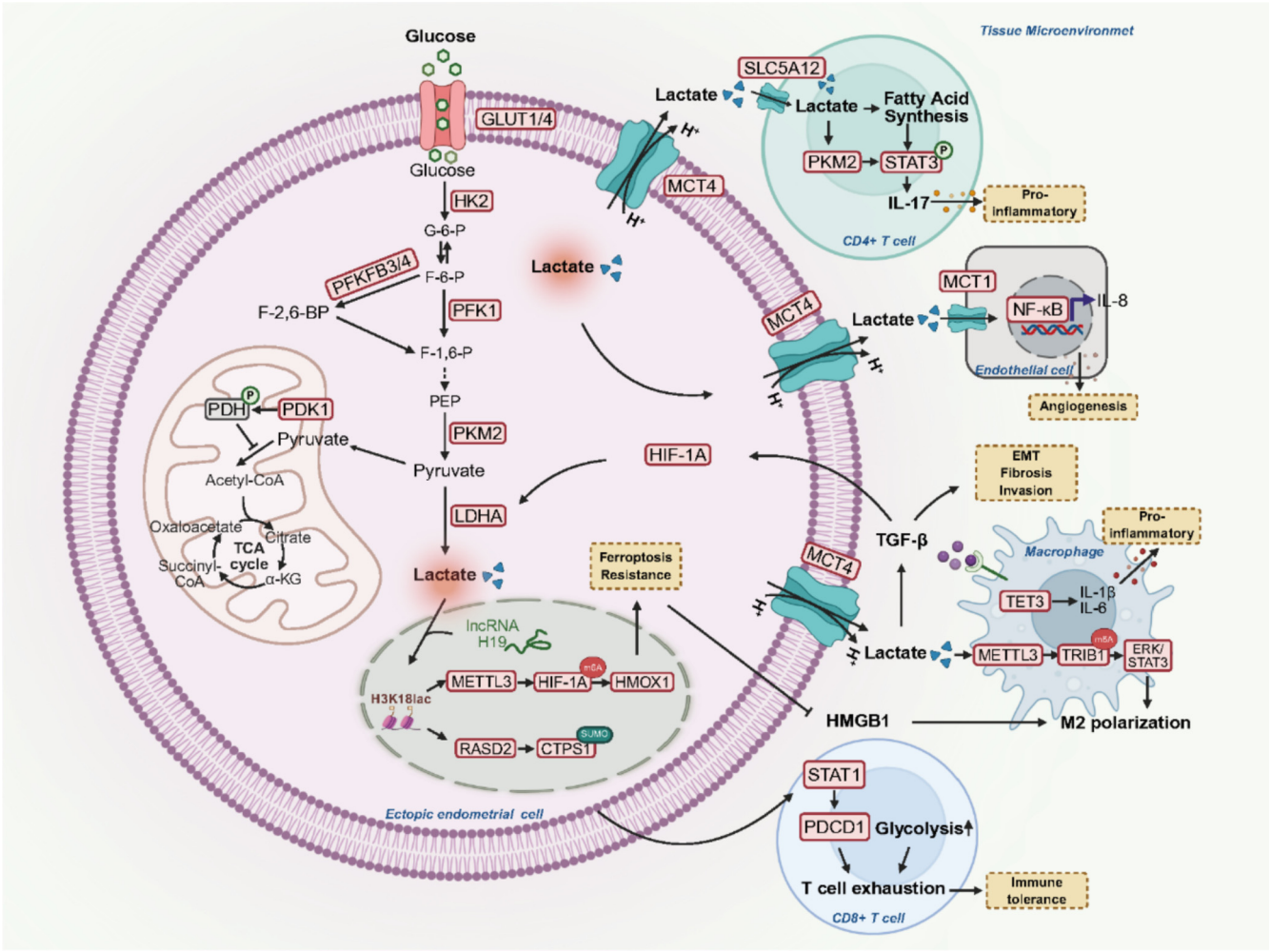

Fig. 1. The mechanism of glucose reprogramming in EMS. Ectopic endometrial cells exhibit a metabolic shift toward glycolysis, characterized by increased glucose uptake, upregulation of glycolytic enzymes (e.g., HK2, PFKFB3/4, PKM2, LDHA), and elevated lactate production. The accumulated lactate promotes disease progression by acidifying the microenvironment, inducing epigenetic modifications, and facilitating crosstalk with immune cells. GLUT1/4, glucose transporter 1/4; MCT1/4, monocarboxylate transporter 1/4; HK2, hexokinase 2; PFKFB3/4, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3/4; PFK1, phosphofructokinase; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; PDK1, pyruvate dehydrogenase kinase 1; PDH, pyruvate dehydrogenase; HIF-1A, hypoxia-inducible factor 1A; METTL3, methyltransferase like 3; HMOX1, heme oxygenase 1; RASD2, ras homolog enriched in striatum; CTPS1, CTP synthase 1; HMGB1, high mobility group box 1; TRIB1, tribbles homologue 1; SLC5A12, solute carrier family 5 member 12; STAT1/3, signal transducer and activator of transcription 1/3; TET3, ten-eleven translocation 3; PDCD1, programmed cell death 1; G-6-P, glucose-6-phosphate; F-6-P, fructose-6-phosphate; F-2,6-BP, fructose-2,6-bisphosphate; F-1,6-P, fructose-1,6-bisphosphate; PEP, phosphoenolpyruvate; α-KG, α-ketoglutarate. Red box, upregulated; Green box, downregulated. The image was created with BioRender.com under a paid license.

tive to oxidative phosphorylation by upregulating glucose transport and glycolytic throughput. Glucose transporters (GLUTs), the "gatekeepers" of cellular glucose entry, are markedly upregulated. GLUT1 expression is significantly upregulated by approximately threefold in ectopic endometrial lesions from patients [15], with specific enrichment of GLUT4 in ectopic endometrial cells [16], highlighting the therapeutic potential of targeting GLUT-mediated uptake.

Hexokinase 2 (HK2), which catalyzes the initial glycolytic step, traps glucose intracellularly as glucose-6-phosphate (G6P) and links glycolysis to ancillary pathways such as the pentose phosphate pathway (PPP). HK2 is consistently upregulated in ectopic lesions of EMS [15,17], correlating with elevated progesterone levels [18]. Silencing HK2 activates signal transducers and activators of transcription (STATs) phosphorylation and suppresses endometrial stromal cell proliferation [19]. Moreover, ALKBH5, an m6A demethylase, enhances HK2 expression in endometrial stromal cells to promote glycolysis, invasion, and migration [20].

The second key step of glycolysis is catalyzed by phosphofructokinase 1(PFK1), whose activity is regulated by allosteric modulators such as fructose-2,6-bisphosphate (F-2,6-BP) [21]. The PFKFB family enzymes (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase) are bifunctional enzymes possessing both kinase and phosphatase domains and are responsible for regulating F-2,6-BP synthesis and degradation [21,22]. PFKFB3 exhibits significantly higher kinase than phosphatase activity, increasing intracellular F-2,6-BP levels and allosterically activating PFK1, thus promoting glycolysis. Clinical tissue analyses revealed that PFKFB3 is highly expressed in endometriotic tissues, and functional experiments in cells further demonstrate that it promotes the EMT in endometrial stromal cells via interaction with β-catenin, thereby enhancing cell migration, invasion, and glycolysis [23]. Notably, the OTUB1/HSF1-PFKFB3 axis represents a core regulatory mechanism governing PFKFB3 expression in endometriosis. OTUB1, as a deubiquitinase, stabilizes heat shock factor 1 (HSF1) protein, which in turn directly transcriptionally activates PFKFB3. This axis has been comprehensively validated across clinical tissue samples, in vitro cell models, and in vivo animal studies, and its activity is significantly positively correlated with lesion progression and invasive potential, making it the primary upstream driver of aber-

rant PFKFB3 upregulation in endometriosis [24,25]. PFKFB4 acts as a "bidirectional regulator", with its kinase activity being particularly important for maintaining aberrant glucose metabolism and cell proliferation. PFKFB4 is highly expressed in ectopic endometrial tissues. Its activity can be enhanced through phosphorylation mediated by proviral insertion in murine lymphomas 2 (PIM2), driving glycolysis and cell proliferation [26]. Conversely, the ubiquitin ligase Hsc70-interacting protein (CHIP) can promote PFKFB4 ubiquitination and degradation, inhibit glycolytic activity, and impede the invasion and migration capabilities of ectopic endometrial cells [27].

Pyruvate kinase M2 (PKM2) is the key enzyme for the final step of glycolysis, catalyzing the conversion of phosphoenolpyruvate to pyruvate. PKM2 is highly expressed in various tumors. Its dimer–tetramer conformational switching affects energy metabolism and participates in the regulation of EMT, invasion, and metastasis through post-translational modifications such as phosphorylation and acetylation [28]. Notably, PIM2 and PAK5 serve as the core upstream drivers of PKM2 activation in endometriosis, whereas NF-κB and FTO play secondary or regulatory roles. PIM2 kinase enhances glycolysis and fibrosis by transcriptionally upregulating PKM2 [29]. P21-activated kinase 5 (PAK5) directly phosphorylates and stabilizes PKM2 to promote glycolysis, proliferation, and metastasis [30]. NF-κB signaling sustains cell survival by inducing PKM2 overexpression, but this effect is more related to stress adaptation rather than a core driving factor [31]. As a negative regulator, the m6A demethylase FTO inhibits glycolysis by targeting PKM2 and also contributes moderately to the pathological progression of EMS [32]. Collectively, the PIM2-PKM2 and PAK5-PKM2 axes represent the dominant and functionally validated mechanisms underlying aberrant PKM2-driven glycolysis in EMS, which are consistently supported by multiple studies. Other regulatory factors mainly play auxiliary or modulatory roles rather than acting as core pathological drivers.

In summary, the synergistic action of key glycolytic enzymes collectively promotes the proliferation, invasion, and survival of ectopic endometrial cells, underscoring glycolysis as a promising therapeutic target.

Aberrant lactate metabolism and its implications

Lactate metabolism represents a critical node in glucose metabolic reprogramming in EMS. Elevated lactate levels are consistently reported in patient ectopic endometrial lesions and peritoneal fluid [9,33]. This shift is largely dependent on the abnormal activation of lactate dehydrogenase A (LDHA), which catalyzes the conversion of pyruvate to lactate and sustains high glycolytic flux. In EMS, peritoneal TGF-β1 concentrations are markedly increased. This cytokine stabilizes HIF-1α expression even under normoxic conditions by suppressing the expression of inhibitor of DNA binding 2 (ID2). HIF-1α subsequently binds to the LDHA promoter, enhancing its transcription and accelerating lactate production. Cell-based functional studies have indicated that silencing LDHA suppresses cell migration and glycolysis, promotes apoptosis, and is associated with reduced expression of pyruvate dehydrogenase kinase 1 (PDK1) [9,34,35]. PDK1, a central mitochondrial regulator, phosphorylates and inactivates pyruvate dehydrogenase (PDH), blocking pyruvate entry into the tricarboxylic acid (TCA) cycle and favoring its conversion to lactate via LDHA, thereby exacerbating lactate accumulation [9,36]. Under hypoxic conditions, HIF-1α further induces PDK1 expression in endometriotic stromal cells, enhancing glycolysis and conferring resistance to oxidative stress-induced apoptosis [37].

Beyond its metabolic role, lactate functions as a substrate for histone lactylation, directly linking metabolism to epigenetic regulation. Zhang et al. first reported that lactate accumulation drives histone lysine lactylation, promoting gene transcription from chromatin [38]. In EMS, ectopic endometrial stromal cells exhibit enhanced glycolysis and lactate enrichment, which elevates H3K18 lactylation, upregulates METTL3, and activates the HIF-1α/HMOX1 pathway, ultimately increasing resistance to ferroptosis. Concurrently, suppression of high mobility group box 1 (HMGB1) expression and secretion promotes macrophage M2 polarization [33]. Cellular mechanistic studies have demonstrated that LncRNA H19 promotes ectopic endometrial cell proliferation and migration through facilitating glycolysis and histone lactylation [39]. Additional evidence implicates the RASD2/CTPS1 axis in lactylation-mediated disease progression [40]. Collectively, histone lactylation emerges as both a biomarker of EMS progression and a mechanistic bridge between metabolic reprogramming and epigenetic remodeling.

Intracellular lactate accumulation is exported via monocarboxylate transporter 4 (MCT4), leading to acidification of the extracellular microenvironment. This activates latent TGF-β1 and further upregulates glycolytic enzymes through a positive feedback loop, inducing myofibroblast differentiation and EMT and enhancing the invasive ability of ectopic endometrial cells [9,35]. Endothelial cells uptake lactate through MCT1, activating NF-κB and upregulating IL-8, which promotes pathological angiogenesis [41,42].

Lactate also reshapes the immune microenvironment in EMS. Studies indicate that Lactate not only directly influences immune cell function but also participates in complex intercellular signaling networks. In $CD4^+$ T cells, Lactate uptake via the SLC5A12 transporter activates the PKM2/STAT3 pathway, promoting IL-17 secretion and fatty acid synthesis, thereby exacerbating inflammatory responses [43]. Additionally, Single-cell sequencing reveals a striking reduction in $CD8^+$ T cells within ectopic lesions, consistent with functional exhaustion. Ectopic endometrial cells can trigger $CD8^+$ T cell metabolic reprogramming via the STAT1/PDCD1 pathway, leading to $CD8^+$ T cell exhaustion [44]. In macrophage regulation, lactate acts as a key metabolic signal. Under hypoxic conditions, endometrial stromal cells enhance glycolysis via the PDPK1-CD47/AKT-LDHA axis, and the resulting lactate promotes macrophage polarization toward an M2 phenotype [45]. Ectopic endometrial cells also secrete lactate to activate the Mettl3/Trib1/ERK/STAT3 signaling pathway in macrophages, further promoting M2 polarization and the proliferation, invasion, and migration of ectopic endometrial cells [46]. Recent studies highlight the epigenetic regulator TET3 as a key player in sustaining pathogenic macrophages. In the lactate-enriched microenvironment of endometriosis, elevated lactate promotes TGF-β1 expression. Notably, TET3 is not only regulated upstream by TGF-β1 and CCL2 but also epigenetically reinforces the expression of these cytokines, forming a positive feed-forward loop. This loop maintains the stability and persistence of pathogenic macrophages, thereby perpetuating the immunosuppressive microenvironment [47,48]. Thus, metabolite-modulated TET3 activity represents a potential critical link connecting metabolic reprogramming to immune microenvironment remodeling in endometriosis. Conversely, macrophages can reinforce glycolytic activity in ectopic endometrial cells by upregulating integrin αvβ3, creating a positive feedback loop between glycolysis and immune remodeling. However, the precise mechanisms remain to be fully elucidated [49].

In conclusion, lactate is far more than a byproduct of glycolysis; it is a key regulator of epigenetic remodeling, intercellular communication, and immune microenvironment reprogramming. Lactate establishes a self-reinforcing positive feedback loop in EMS. Initial pathological stimuli, such as hypoxia or TGF-β1, induce glycolysis and lactate production. However, lactate via matrix acidification, TGF-β1 activation, histone lactylation induction, and immune-cell reprogramming (promoting M2 macrophage polarization), creates a microenvironment more conducive to lesion survival and pro-

gression. Consequently, lactate is not merely a consequence of metabolic reprogramming but a central driver of the malignant progression of the disease.

Lipid metabolic remodeling

Lipids (including sphingolipids, phospholipids, and glycerolipids) are central to energy storage, membrane architecture, signaling, and metabolic regulation. Lipidomics studies have revealed significant alterations in lipid profiles within the ectopic lesions, plasma, and peritoneal fluid of patients with EMS [13,50–52]. This indicates that lipid metabolic network remodeling is a key driver of the transition from eutopic to ectopic endometrial phenotypes.

Clinical epidemiological investigations further indicate that patients with EMS frequently exhibit characteristic dyslipidemia, characterized by elevated levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), non-high-density lipoprotein (non-HDL), and reduced HDL to TC ratio [53]. Moreover, the cardiometabolic index shows a linear association with EMS risk. When this index exceeds 0.67, each unit increase raises the risk by 20% [54]. Additionally, remnant cholesterol, as a novel lipid marker, increases EMS risk by 135% per unit increase [55]. These findings indicate an established clinical association between EMS and dyslipidemia.

These abnormalities in circulating metabolites are not isolated phenomena; rather, they reflect the systemic manifestations of active local metabolic reprogramming within the lesions. The active cell proliferation, anti-apoptotic signaling, inflammatory signaling, and persistent neural remodeling at the lesion site lead to the abundant production of bioactive lipid mediators, such as S1P, within the lesion microenvironment [56]. These metabolites and their precursors may be released into the bloodstream, contributing to the observed changes in the plasma lipid profile. Conversely, systemic dyslipidemia can also act on lesions via the circulatory system, providing additional lipid precursors for lesion cells [13] or creating a systemic environment of low-grade inflammation [57] that affects immune cell function [58], thereby fostering systemic conditions that favor lesion growth. Furthermore, as a minimally invasive source of samples, endometrial fluid exhibits distinct trends in various lipid metabolites compared to other samples, highlighting the uniqueness of its metabolic profile. Unlike serum, its lipid composition more directly reflects the pathophysiological state of the endometrium, rather than indirect systemic changes [59]. It is noteworthy that the serum and follicular fluid lipid metabolic profiles of ovarian endometriosis and deep infiltrating endometriosis (DIE) are phenotype-specific. Ovarian endometriosis exhibits greater accumulation of ketone body metabolites [60,61]. This pattern may be related to higher estrogen levels and supports the notion that different lesion entities possess distinct metabolic phenotypes. This, in turn, may be reflected in different patterns of systemic metabolic abnormalities.

Metabolomic evidence offers further mechanistic insights. Plasma acylcarnitine levels are elevated in EMS, reflecting incomplete fatty acid oxidation [62]. The follicular fluid, however, showed a reduction in short-chain acylcarnitines, suggesting an imbalance in local fatty acid metabolism [63]. Conversely, a higher glycerol-to-palmitoylcarnitine ratio is associated with reduced disease risk. This ratio captures the balance between lipolysis and fatty acid oxidation. A higher ratio suggests that enhanced lipolysis better accommodates inflammatory stress, lowering susceptibility [10].

At the molecular level, bioinformatic analyses have identified 17 differentially expressed fatty acid metabolism-related genes in ectopic endometrial tissues, significantly enriched in arachidonic acid and fatty acid metabolic pathways. However, their mechanistic roles in EMS pathogenesis warrant further investigation [64].

Sphingolipid metabolism

Among these alterations, dysregulated sphingolipid metabolism has emerged as particularly compelling, indicating its pivotal role in driving EMS initiation and maintenance (Fig. 2). Beyond their structural role in membranes, sphingolipids function as bioactive signaling molecules that regulate cellular and tissue homeostasis through lipid–lipid and lipid–protein interactions [65]. Ceramide (Cer) and sphingosine-1-phosphate (S1P) are central and play crucial roles within the sphingolipid metabolic network.

Cer, a pro-apoptotic second messenger, governs differentiation, proliferation, apoptosis, and migration. Its glycosylated derivative, glucosylceramide (GlcCer), exerts mitogenic and anti-apoptotic effects. GlcCer accumulation is implicated in conditions such as polycystic kidney disease [66] and Gaucher disease [67]. Glucosylceramide synthase, the key enzyme balancing Cer and GlcCer, is aberrantly upregulated in EMS, leading to excessive GlcCer accumulation in serum, peritoneal fluid, and endometrial tissue, which promotes the abnormal proliferation and apoptosis resistance of endometrial cells [12]. Another study indicated that long-chain GlcCer can promote endometrial stromal cell migration via interaction with the SDF-1α-CXCR4-LYNpTyr396 axis, creating a microenvironment favorable to ectopic implantation [68].

Several lipid metabolites have been proposed as potential EMS biomarkers, particularly phosphatidylcholine (PC) and sphingomyelin (SM), which are associated with apoptosis resistance [13]. PC, as a marker of highly proliferative states, abnormally accumulates in ectopic endometrial tissues and can promote lysophosphatidic acid (LPA) generation through phospholipase A2 activation [50]. LPA, mediated by LPAR1/3, induces cathepsin B secretion, enhancing the invasive capacity of ectopic endometrial cells. This effect can be reversed by the LPAR1/3 specific inhibitor Ki16425 [69]. Moreover, while sphingomyelin synthase 1 (SMS1) and sphingomyelinase 3 (SMPD3) are upregulated in endometriotic tissues, no significant difference is observed in serine-palmitoyl transferases (SPTL1–3). This indicates that SM hydrolysis rather than de novo synthesis is the major source of Cer. PC can transfer its phosphocholine group to Cer under the catalysis of SMS1 to synthesize SM [12]. Elevated SM levels are also linked to persistent neural remodeling in ectopic lesions, suggesting a role in EMS-associated chronic pain [13].

S1P is the most bioactive sphingolipid metabolite, with its pathological effects governed by the dynamic balance between sphingosine kinases (SPHKs) and degradative enzymes (S1P phosphatase and S1P lyase). S1P concentration is significantly elevated in ovarian endometriotic cysts due to SPHKAP upregulation and decreased S1P degradation [56]. S1P activates the ERK5 pathway via S1PR1/3, inducing ROS-dependent inflammatory responses [70]. S1P can also activate the ERK1/2 pathway via S1PR3 and synergize with TGF-β1 signaling to jointly drive EMT and fibrosis processes in ectopic endometrial cells [71,72]. In addition, S1P signaling mediates the pro-invasive phenotype induced by neuropeptide S in endometriotic cells [73]. Regarding angiogenesis, estrogen enhances S1P synthesis by activating SPHK1, which promotes pathological neovascularization via S1PR1 signaling, providing nutritional support for ectopic lesion growth [74].

Importantly, as S1P is abundant in erythrocytes and platelets [75], elevated peritoneal S1P levels in EMS are closely linked to retrograde menstruation. Excess S1P polarizes peritoneal macrophages toward the M2 phenotype, inducing COX2 expression and PGE2 overproduction while inhibiting macrophage autophagy activity. This process impedes the clearance of refluxed menstrual blood, leading to persistently high S1P concentrations in the peritoneal fluid of patients with EMS even during non-menstrual periods, forming a self-sustaining vicious cycle [76]. Additionally, macrophage-derived IL-1β and TGF-β activate the SPHK1–S1P–S1PR1/2/3 axis, driving ectopic endometrial cell proliferation and

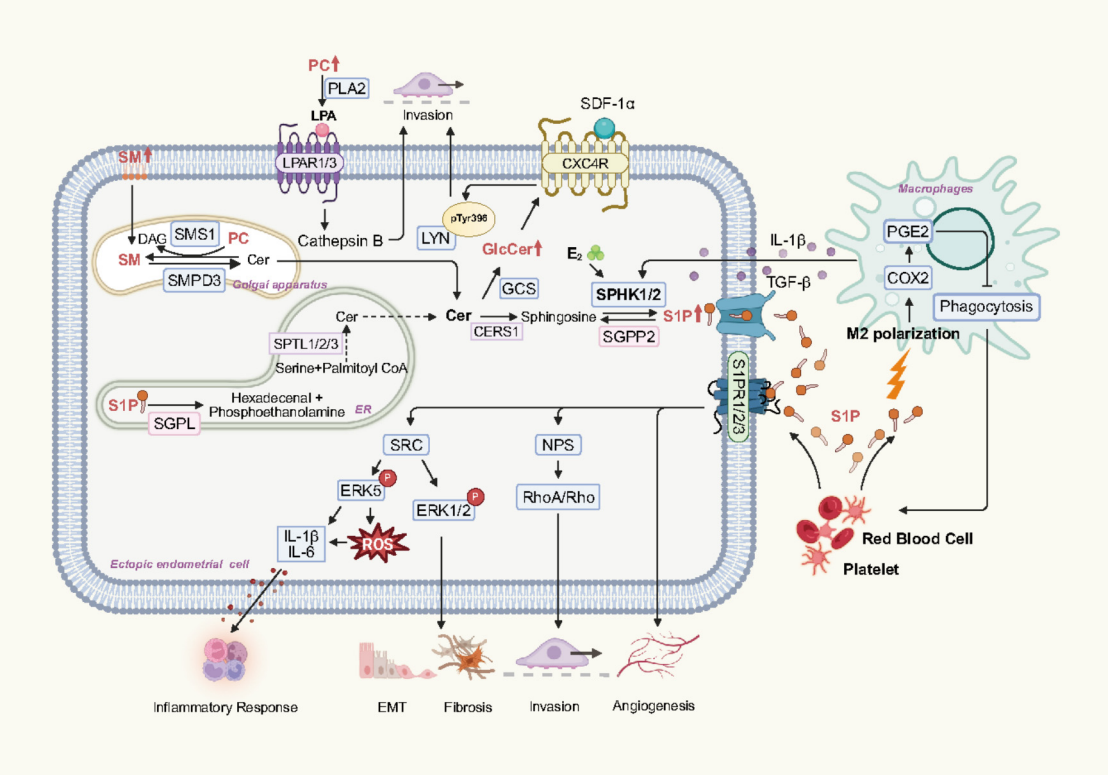

Fig. 2. Dysregulated sphingolipid metabolism in EMS. The balance between pro-apoptotic Cer and pro-proliferative GlcCer, governed by GCS, is shifted towards GlcCer accumulation, promoting ectopic endometrial cell survival and proliferation. Concurrently, S1P levels are elevated due to increased synthesis and decreased degradation. S1P signaling through S1PRs drives inflammation, fibrosis, angiogenesis, and immune suppression (e.g., M2 macrophage polarization), facilitating disease progression. SM, sphingomyelin; SMPD3, sphingomyelinase 3; SMS1, sphingomyelin synthase 1; SPTL1/2/3, serine-palmitoyl transferases 1/2/3; GCS, glucosylceramide synthase; PC, phosphatidylcholine; PLA2, phospholipase A2; CERS1, ceramide synthase 1; LPA, lysophosphatidic acid; LPAR1/3, LPA receptors 1/3; DAG, diacylglycerol; CXCR4, CXC chemokine receptor 4; SDF-1α, stromal cell-derived factor-1α; LYN, tyrosine kinase; Cer, ceramide; GlcCer, glucosylceramides; S1P, sphingosine-1-phosphate; SPHK1/2, sphingosine Kinase 1/2; SGPP2, sphingosine-1-phosphate phosphatase; SGPL, sphingosine-1-phosphate lyase; S1PR1/2/3, sphingosine-1-phosphate receptor 1/2/3; NPS, neuropeptide S; E_2, estrogen; ROS, reactive oxygen species; EMT, epithelial-mesenchymal transition. Blue box, upregulated; Pink box, downregulated. The image was created with BioRender.com under a paid license.

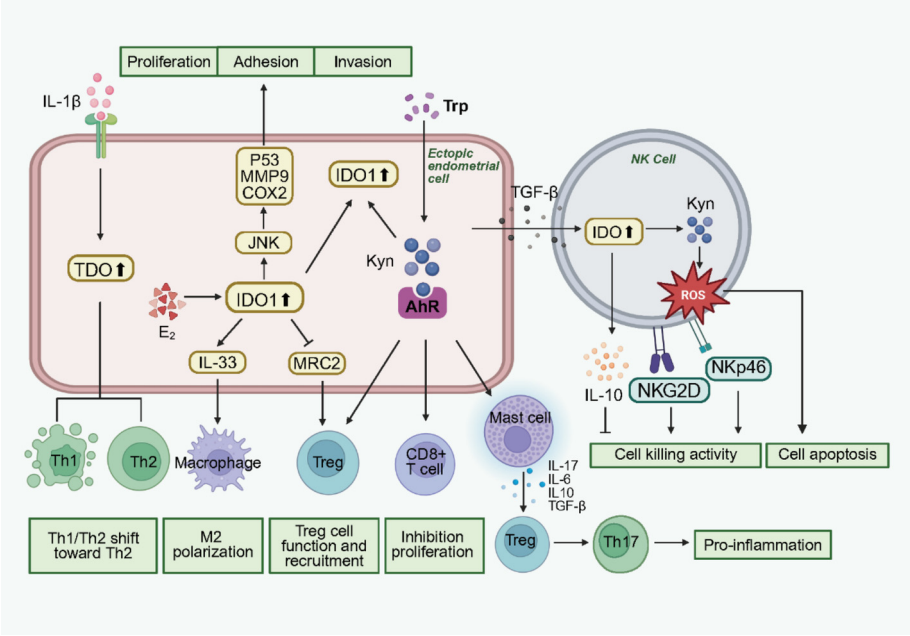

Fig. 3. The tryptophan-kynurenine axis drives immunosuppression in EMS. Hyperactivation of the kynurenine pathway, mediated by IDO1/TDO, depletes tryptophan and accumulates kynurenine in EMS. This metabolic rewiring directly suppresses cytotoxic NK and T cell function while promoting pro-survival signaling in ectopic endometrial cells. The resulting immunosuppressive microenvironment enables ectopic lesions to evade immune clearance and thrive. Trp, tryptophan; TDO, tryptophan 2,3-dioxygenase; IDO1, indoleamine 2,3-dioxygenase 1; Kyn, kynurenine; AhR, aryl hydrocarbon receptor; E_2, estrogen; MMP9, matrix metalloproteinase 9; MRC2, mannose receptor C-type 2; ROS, reactive oxygen species. The image was created with BioRender.com under a paid license.

IL-6 secretion to establish a pro-inflammatory microenvironment [77].

Collectively, these findings highlight extensive remodeling of lipid metabolic networks in EMS, whereby lipid intermediates and metabolites regulate proliferation, invasion, apoptosis resistance, angiogenesis, and immune microenvironment reconstruction, ultimately driving ectopic lesion establishment and progression.

Cholesterol metabolism

Lipid metabolism is profoundly reprogrammed in EMS, with cholesterol dysregulation acting as a key driver of a hyperestrogenic niche. Homeobox A10, a cholesterol synthesis inhibitor, is abnormally lowly expressed in ovarian ectopic endometrial stromal cells. Its deficiency directly leads to upregulated expression of cholesterol synthesis-related genes [78]. Intracellular cholesterol levels are markedly and consistently higher in ectopic stromal cells than in normal endometrial stromal cells. Accumulated cholesterol activates steroidogenic enzymes (CYP11A1, CYP17A1, and CYP19A1), resulting in elevated local estradiol levels. Elevated estradiol in turn induces prion protein expression. This suppresses PPARα, upregulating HMGCR to enhance cholesterol synthesis and simultaneously inhibiting ABCA1-mediated cholesterol efflux. This dual effect further drives cholesterol accumulation and estradiol biosynthesis, fueling ectopic endometrial cell proliferation, invasion, and migration, and establishing a self-reinforcing estrogen–cholesterol positive feedback loop [79].In summary, lipid metabolic networks are profoundly reprogrammed in EMS. Lipids and their metabolites modulate proliferation, invasion, apoptosis resistance, angiogenesis, and immune microenvironment remodeling, synergistically driving lesion establishment and progression.

Amino acid metabolic reprogramming

Amino acids, as the building blocks of proteins, are essential for the synthesis of nucleotides, glutathione, and other biomolecules. Metabolomic studies have demonstrated significantly reduced serum concentrations of multiple amino acids in patients with EMS, including glutamine, valine, threonine, histidine, tyrosine, leucine, isoleucine, and glutamate. These reductions correlate with heightened inflammation and oxidative stress, leading to increased amino acid oxidation and metabolic demand, ultimately causing systemic amino acid depletion [61,80]. Many of these reduced amino acids are glucogenic, and their decline reflects an insufficient glucose supply to meet the energy requirements of rapidly proliferating cells. Consequently, enhanced gluconeogenesis compensates for high energy consumption, a metabolic feature reminiscent of cancer cells [81]. In addition, enhanced catabolism of leucine and isoleucine replenishes TCA cycle intermediates such as citrate via acetyl-CoA, providing carbon skeletons and energy to ectopic lesions [61,82]. Interestingly, elevated serum lysine and reduced arginine levels have also been observed in EMS [82]. Lysine, an essential amino acid with antioxidant properties, may increase as a compensatory mechanism against oxidative stress. Reduced arginine levels could be due to competitive uptake via the SLC7 family of transporters, favoring preferential arginine utilization by ectopic endometrial cells [51].

Tryptophan metabolism

Within the broader context of active amino acid metabolism, tryptophan—a strictly essential amino acid—plays a pivotal role in regulating the immune microenvironment and supporting ectopic endometrial cell survival (Fig. 3). Patients with EMS exhibit reduced serum tryptophan levels [83]. Targeted metabolomics in nonhuman primate models have similarly shown significantly reduced tryptophan levels in ectopic endometrial tissues [84]. Approximately 95% of tryptophan is catabolized via the KYN pathway, regulated by two rate-limiting enzymes: indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). This pathway contributes to inflammation and immune modulation in diverse diseases [85]. In EMS, inflammatory cytokine IL-1β enhances TDO activity in ectopic endometrial stromal cells, accelerating tryptophan catabolism and inducing selective Th1 apoptosis. This favors a Th2-dominant milieu, which promotes disease progression [86–88]. Moreover, IDO1 expression is significantly upregulated, driving the proliferation, adhesion, and invasion of endometrial stromal cells through JNK-mediated regulation of P53, MMP9, and COX2 [89,90]. Estrogen further induces IDO1 expression, suppressing mannose receptor C type 2 and promoting regulatory T cell (Treg) differentiation, creating an immune-tolerant environment conducive to disease development [91]. IDO1 overexpression also induces ectopic endometrial stromal cell-derived IL-33, which promotes M2 macrophage polarization, reduces the antigen-presenting molecules HLA-DR and CD11c, and diminishes phagocytic function, ultimately facilitating lesion survival [92].

KYN, as an endogenous ligand of the aryl hydrocarbon receptor (AhR), amplifies tryptophan depletion through the KYN/AhR-IDO positive feedback loop. This suppresses $CD8^+$ T cell proliferation, enhances Treg differentiation, and inhibits effector T cell activation, thereby creating an immunosuppressive microenvironment [93,94]. Simultaneously, KYN/AhR can activate mast cells to release cytokines such as IL-17, IL-6, IL-10, and TGF-β, driving the conversion of Treg cells into chronic inflammatory Th17 lymphocytes and exacerbating the EMS inflammatory response [95,96]. NK cell metabolism is also disrupted: ectopic stromal cells secrete high levels of TGF-β, which induces IDO in NK cells. This leads to reduced NKG2D/NKp46 expression, elevated IL-10, impaired cytotoxicity, and IDO-mediated L-KYN accumulation, inducing NK cell apoptosis via ROS signaling. These alterations compromise NK cell-mediated clearance of ectopic endometrial stromal cells and facilitate lesion formation [97,98].

Collectively, tryptophan metabolism plays a central role in immune remodeling in EMS, with IDO and TDO emerging as potential therapeutic targets.

Glutamine metabolism

Glutamine, the most abundant and highly consumed free amino acid, is critical in disease-associated metabolic reprogramming. Second only to glucose in energy provision, glutamine metabolism supports macromolecule biosynthesis, signaling regulation, and redox homeostasis [99]. In EMS, enhanced aerobic glycolysis diverts pyruvate to lactate rather than the TCA cycle, while ectopic cells increase demand for biosynthetic precursors and NADPH. To compensate, ectopic endometrial cells exhibit elevated glutaminolysis, resulting in significantly reduced glutamine levels within the lesions [100]. Glutamine uptake via SLC1A5 is followed by glutaminase-mediated conversion to glutamate, which is further metabolized to α-ketoglutarate to sustain the TCA cycle. This process not only provides ATP and biosynthetic precursors but also promotes survival by modulating mTOR signaling and redox balance [99]. Recent studies revealed that lncRNA urothelial carcinoma associated 1 enhances glutamine metabolism through the IGF2BP3/c-MYC/GLS1 axis, promoting ectopic endometrial stromal cell proliferation and migration [14].

Glutamine-derived glutathione, a key antioxidant, mitigates ROS accumulation, assisting the adaptation of ectopic endometrial cells to oxidative stress [101]. Microbiome analysis has shown reduced abundance of *Tuzzerella* in ectopic tissues, correlating with decreased local glutamine levels and complement C7 upregulation, which promotes Treg infiltration [100].

Notably, hematopoietic cellular kinase (HCK) expression is significantly downregulated in macrophages from patients with EMS, closely linked to elevated estrogen levels. HCK deficiency reduces intracellular glutamine, enhances autophagy, impairs phagocytosis, and diminishes macrophage clearance of ectopic cells. This ultimately accelerates disease progression [102].

Glutamine metabolism and proline biosynthesis are likewise interconnected. Proline can be synthesized from glutamine via multiple enzymatic steps, while oncogene c-MYC suppresses the POX/PRODH pathway, blocking proline-to-glutamine conversion and potentially explaining the elevated proline/glutamine ratio in patient serum. Conversely, collagen degradation-derived proline can replenish the glutamate pool via the PRODH-P5CDH axis, creating a positive feedback loop between metabolism and matrix remodeling, which promotes lesion fibrosis [103–105].

In conclusion, amino acid metabolic reprogramming in EMS drives disease progression by supporting cell proliferation, providing energy substrates, and creating an immunosuppressive microenvironment.

Glucose, lipid, and amino acid metabolism crosstalk

In EMS, glucose, lipid, and amino acid metabolism do not operate independently but are interwoven into a highly integrated and synergistic network, which collectively drives ectopic lesion establishment and progression. This process is systematically regulated by the hypoxia-inducible factor (HIF) signaling pathway, the PI3K/Akt/mTOR pathway, the Myc transcription factor network, and so on. HIF-1α is stably expressed in the hypoxic microenvironment, activating genes related to glycolysis [9,34,37] and angiogenesis [106]. Abnormal activation of the PI3K/Akt/mTOR pathway, often triggered by PTEN loss, not only enhances glycolysis but also promotes macrophage M2 polarization, exacerbating immune suppression [107,108]. High expression of c-MYC [109] further strengthens glycolysis, glutamine metabolism, and lipid synthesis to support the high proliferative demands of cells [14,109–112]. These pathways constitute a highly interconnected regulatory network which underpins extensive metabolic rewiring in EMS, enabling ectopic endometrial cells thrive under metabolic stress.

Notably, enhanced aerobic glycolysis provides rapid energy and generates diverse intermediate metabolites, which fuel other biosynthetic pathways. G6P, the entry point of the PPP, produces NADPH, which is essential for lipid synthesis and maintaining redox balance, including glutathione production [113]. Glycolytic intermediate 3-phosphoglycerate serves as a precursor for the synthesis of amino acids crucial for protein and glutathione biosynthesis (serine, glycine, and cysteine). Lactate accumulation acidifies the microenvironment and activates latent TGF-β1, which promotes fibrosis and sphingolipid metabolism, exacerbating disease progression [9,35,77].

Abnormal cholesterol metabolism provides precursors for local estrogen synthesis; estrogen signaling can in turn regulate the key tryptophan metabolic enzyme IDO1, forming an immunosuppressive microenvironment [91]. Estrogen also stabilizes HIF-1α expression, further promoting glycolysis [106].

Metabolic reprogramming in EMS constitutes a hierarchicale-volving network. Glycolysis acts as the central hub that initiates this vicious cycle. The energy, biosynthetic precursors, and lactate signaling derived from glycolysis underlie lipid synthesis and the establishment of an immunosuppressive microenvironment. In contrast, pathways such as amino acid metabolism play an amplifying role in sustaining the chronicity of the disease. These interconnected pathways construct a metabolic microenvironment which supports ectopic cell proliferation, invasion, resistance to cell death, and immune evasion, establishing a ‘‘malignant metabolic cycle” which fuels disease progression.

Metabolic reprogramming of granulosa cells in EMS-associated infertility

Infertility is one of the most common complications of EMS, exerting profound effects on patient physical and psychological well-being. Although the underlying mechanisms remain incompletely understood, current evidence indicates that impaired follicular development and reduced oocyte quality constitute the main pathological basis of EMS-associated infertility [114,115]. Within the follicle, cumulus granulosa cells and mural granulosa cells cooperate to support oocyte maturation. Normal glucose and lipid metabolism is crucial for maintaining granulosa cell function and follicular development; thus, metabolic dysregulation in granulosa cells disrupts oocyte growth and competence.

Metabolic reprogramming in EMS granulosa cells

Granulosa cells from patients with EMS exhibit significant metabolic reprogramming characterized by altered glucose metabolism. Upregulation of GLUT1, phosphofructokinase-M, phosphoglycerate kinase 1, and LDHA, along with downregulation of the TCA cycle enzyme citrate synthase, suggests enhanced glucose uptake, elevated glycolysis, and attenuated oxidative phosphorylation. This glycolysis-dominant phenotype may represent an adaptive response to prevent premature apoptosis; however, it is closely associated with reduced oocyte quality [116].

Abnormal glucose metabolism is tightly coupled with mitochondrial dysfunction. EMS granulosa cells exhibit reduced ATP production, decreased mitochondrial membrane potential, and excessive ROS accumulation [116,117]. Transcriptomic profiling further reveals that oxidative phosphorylation, mitochondrial function, and steroid biosynthesis pathways are dysregulated in cumulus cells, correlating with defective oocyte maturation [118]. Latest single-cell and spatial transcriptomics have identified that granulosa cells exhibit abnormal iron metabolism, and iron overload can induce cellular senescence, intensified glycolysis, and mitochondrial injury [115].

Granulosa cells from patients with EMS also exhibit disrupted lipid metabolism, mainly in steroidogenesis and sphingolipid pathways. Downregulation of cytochrome P450 aromatase expression affects estrogen synthesis and activates granulosa cell apoptosis pathways [119,120]. Meanwhile, upregulation of genes related to ceramide synthesis (CERS1, SPTLC1, SMPD1) [121] and the accumulation of palmitic acid [122,123] further promote cumulus granulosa cell apoptosis [121,123].

In summary, metabolic reprogramming of granulosa cells in EMS is characterized by enhanced glycolysis, impaired mitochondrial function, and lipid metabolism imbalance. These three factors interact and collectively lead to insufficient energy supply, increased oxidative stress, abnormal hormone synthesis, and heightened cell apoptosis in granulosa cells.

Impact of granulosa cell metabolic reprogramming on oocyte maturation

Oocytes rely heavily on granulosa cells for energy and antioxidant support due to their intrinsically low expression of GLUTs and PFK [124–126]. In EMS, enhanced glycolysis in granulosa cells leads to insufficient energy supply and weakened antioxidant capacity, accompanied by abnormal accumulation of lactate and iron ions. This exposes oocytes to acidic environments and oxidative stress, resulting in meiotic arrest, incomplete cytoplasmic maturation, and mitochondrial dysfunction [115,127]. Furthermore, iron overload may also trigger ferroptosis and impair oocytes via exosome transfer of abnormal miRNAs [128].

Single-cell RNA-seq reveals the enrichment of differential genes related to oxidative stress, mitochondrial function, and steroid metabolism in oocytes from patients with EMS. Among them, the oxidative stress-related gene dual specificity phosphatase 1 is significantly upregulated, affecting oocyte development and maturation, spindle assembly, and chromosome alignment by inhibiting mitogen-activated protein kinase pathway activity [129,130]. The upregulated steroid metabolism-related gene APOE increases lipid metabolism within the oocyte, exacerbating oxidative stress and impairing oocyte quality [131]. Additionally, Cer accumulation alters mitochondrial permeability and inhibits oxidative phosphorylation, further restricting oocyte maturation [132].

Thus, EMS leads to metabolic reprogramming in granulosa cells, iron homeostasis imbalance, and accumulation of lipid toxicity, which synergistically disrupt the energy and redox balance of the oocyte, impairing its maturation and developmental potential.

Follicular fluid metabolism in EMS-associated infertility

Follicular fluid (FF), the shared microenvironment of oocytes and granulosa cells, reflects both systemic and local ovarian metabolism while directly influencing oocyte maturation. Metabolomics reveals that patients with EMS exhibit reduced glucose and citrate but increased lactate and pyruvate levels in the FF, consistent with enhanced glycolysis in granulosa cells. This can also be interpreted as metabolic reprogramming triggered by the inflammatory microenvironment [60,133]. Simultaneously, untargeted metabolomics study revealed abnormalities in the steroid hormone biosynthesis and glycerophospholipid metabolism pathways in the FF of patients with EMS. Phosphatidylinositol (PI) levels were increased, and lysophosphatidylinositols (LPI) levels were decreased. Increased PI and a decreased LPI/PI ratio were associated with reduced numbers of retrieved and mature oocytes [134]. LPI, as an endogenous ligand for the G protein-coupled receptor 55, can activate ERK phosphorylation and promote cumulus–oocyte complex expansion and oocyte maturation [135,136]. LPI is considered a potential adjunctive factor for improving EMS-related oxidative stress [134].

Abnormal oxidized lipid levels can be observed in the FF of patients with EMS; the concentration of epoxyeicosatrienoic acids (EETs), particularly 14,15-EET, is significantly reduced. This is associated with poor assisted reproductive technology outcomes. Reduced 14,15-EET concentration also leads to decreased antioxidant capacity in granulosa cells, reduced ATP generation, ROS accumulation in oocytes, and abnormal COC expansion, resulting in reduced fertility. Supplementation with 14,15-EET has been shown to ameliorate granulosa cell senescence and enhance reproductive outcomes by suppressing aberrant activation of the PI3K–AKT–mTOR signaling pathway [137].

Furthermore, cyclic bleeding from ectopic lesions may release heme into the FF, causing iron overloads which damage granulosa cells, impair WNT/β-catenin signaling, and hinder oocyte maturation and ovulation. Notably, FF iron levels may serve as predictive markers for IVF outcomes [115].

In summary, metabolic reprogramming of granulosa cells in EMS—characterized by glycolysis enhancement, mitochondrial dysfunction, lipid dysregulation, and iron overload—disrupts oocyte energy supply and redox homeostasis, impairing maturation and developmental potential. FF abnormalities exacerbate this unfavorable microenvironment. Targeting granulosa cell metabolism (e.g., glycolysis inhibitors, iron chelators, and antioxidants such as EET analogs or LPI), optimizing FF composition represent potential strategies to improve oocyte quality and fertility outcomes in EMS-associated infertility.

Advances in metabolic targeted therapy for EMS

Metabolic reprogramming in EMS sustains the high energy demands of ectopic lesions and establishes an immune-suppressive and pro-inflammatory microenvironment. Consequently, therapeutic interventions targeting metabolic pathways have increasingly garnered attention (Table 2).

Targeting glucose metabolic pathways

PDK inhibitors

Dichloroacetate (DCA), a selective PDK inhibitor, restores PDH activity by targeting PDK1, reducing lactate accumulation in the peritoneal fluid and inducing ROS-dependent apoptosis [138,139]. Oral DCA administration significantly reduced lesion size in animal models [37,139]. A single-arm clinical trial (NCT04046081) has been initiated to evaluate the effectiveness and acceptability of DCA in treating endometriosis-associated pain [140] Certain natural compounds also show PDK-targeting potential. Caesalpinia sappan extract selectively inhibits PDK1, suppresses glycolysis, and triggers mitochondrial ROS-mediated apoptosis in ectopic epithelial cells while sparing normal stromal cells [141]. However, its active compound brazilin exhibits reproductive toxicity, necessitating further safety assessments [142]. Prunella vulgaris induces apoptosis in ectopic endometrial cells and modulates glycolytic metabolism through dual inhibition of PDK1/3 and LDHA activities [143]. Notably, its established application in cancer therapy [144], coupled with its anti-estrogenic effects [145], suggests considerable promise for treating EMS.

PFKFB inhibitors

PFKFB3 inhibition with PFK15 effectively suppresses ectopic stromal cell migration and lesion growth in mice [23]. Its derivative, PFK158, a PFKFB3 inhibitor to undergo Phase I clinical evaluation (NCT02044861), demonstrated favorable tolerability [146]. In addition, KRIBB11, an HSF1 inhibitor, indirectly downregulates PFKFB3 expression, leading to a reduction in cell proliferation and lesion progression [24,25]. The PFKFB4 inhibitor 5MPN has also shown significant therapeutic efficacy in both in vitro and in vivo models [27].

Other glycolysis-related targets

Other glycolysis-related targets are implicated in EMS. Agents such as 2-deoxyglucose and the ALKBH5 inhibitor 5-Carboxy-8-hydroxyquinoline (IOX1) inhibit HK2 and reduce ectopic lesion burden [20]. The PIM2 inhibitor SMI-4a [29], cinnamic acid [31], and PAK5 inhibitor GNE2861 [30] reduce PKM2 activity/stability, limiting proliferation and fibrosis. Aurora kinase A inhibitor alisertib [147] and CHIP agonist YL-109 [148] attenuate glycolysis through distinct mechanisms. Combination therapy with atorvastatin and resveratrol blocks glucose and lactate transport, impairing lesion growth and angiogenesis [41]. However, statins carry potential adverse effects on ovarian function, steroidogenesis and fertility. Given the lack of reproductive safety data, statins should currently be reserved for EMS patients with no plans for childbearing [149].

These findings highlight glycolysis as a key metabolic vulnerability in EMS. Thus, targeting PDKs, PFKFB isoforms, and other glycolysis-related regulators offers multiple therapeutic entry points. However, translation of these strategies into routine therapy requires further studies to optimize selectivity and evaluate long-term reproductive safety.

Targeting lipid metabolism

Targeting the SPHK–S1P–S1PR axis

The SPHK–S1P–S1PR axis, already explored in cancer and autoimmune diseases, is an emerging target in EMS. Current interventions

Table 2
Preclinical studies on targeting metabolic pathways for endometriosis therapy.

Drug name	Target metabolite/ protein	Mechanism of action	Adverse effects	Ref.
Targeting glucose metabolic pathways				
DCA	PDK1	Inhibits PDK1 to restore PDH activity, resulting in reduced lactate production, decreased oxygen consumption, and induced apoptosis.	Peripheral neuropathy; Fatigue and Nausea; Hepatic toxicity.	[37,138,139,166]
Caesalpinia sappan	PDK1	Inhibits PDK1 expression to suppress glycolysis and activate ROS-mediated apoptosis.	Reproductive toxicity; Contact dermatitis.	[141,142,167]
Prunella vulgaris	PDK1/3 and LDHA	Suppresses aerobic glycolysis and induces mitochondrial apoptosis in ectopic endometrial cells via dual inhibition of PDK1/3 and LDHA.	Gastrointestinal symptoms and contact dermatitis.	[143,168]
PFK15	PFKFB3	Inhibits glycolysis in both ectopic endometrial epithelial and stromal cells, reducing their migration/invasion capabilities and suppressing lesion growth by targeting PFKFB3.	No significant adverse effects reported.	[23,169]
KRIBB11	HSF1	Suppresses ectopic endometrial cell growth by inhibiting HSF1 to downregulate the key glycolytic enzyme PFKFB3.	No significant adverse effects reported.	[25,170]
5MPN	PFKFB4	Inhibits proliferation, invasion, and migration of ectopic endometrial cells, and suppresses ectopic lesion formation in mice by targeting PFKFB4.	–	[27]
IOX1	ALKBH5	IOX1 reduces the number and size of ectopic lesions in mice by inhibiting ALKBH5 and HK2.	–	[20]
SMI-4a	PIM2	Inhibits glycolysis and fibrosis in endometriotic cells by targeting PIM2 to downregulate PKM2 expression.	–	[29]
Cinnamic acid	PKM2	Inhibits viability, invasion, and glycolysis in endometrial stromal cells by suppressing NF-κB-induced PKM2 transcription.	No significant adverse effects reported.	[31,171]
GNE2861	PAK5	Suppresses glycolysis, invasion, and migration of endometriotic cells by inhibiting PAK5 activity to reduce PKM2 phosphorylation.	–	[30]
Alisertib	AURKA	Inhibits glycolysis, proliferation, invasion, and migration of ectopic endometrial cells, and reduces ectopic lesion burden in mice by Inhibiting AURKA activity.	Myelosuppression, fatigue and mucositis.	[147,172]
YL-109	CHIP	Suppresses proliferation, invasion, and glycolysis of ectopic endometrial cells by upregulating CHIP to promote HMGB1 ubiquitination and degradation.	–	[148]
Atorvastatin + Resveratrol	GLUTs and MCTs	Synergistically inhibits GLUTs and MCTs expression, blocking glucose uptake and lactate transport, thereby inhibiting angiogenesis.	Atorvastatin: Myopathy; Adverse effects on gonadal activities, steroidogenesis, and fertility function. Resveratrol: Nausea, diarrhea, fatigue, and renal toxicity.	[41,149,173,174]
Targeting lipid metabolism				
SKI-5C	SPHK1	Inhibits angiogenesis and suppresses ectopic lesion progression by specifically targeting SPHK1.	No significant adverse effects reported.	[74,175]
S1P-neutralizing antibody	S1P	Neutralizes S1P biological function, blocking its induction of cell proliferation and pro-angiogenic factor release.	–	[150]
FTY720	S1PRs	Reduces immune cell infiltration into lesions by antagonizing S1PR1, thereby inhibiting inflammation and fibrosis progression.	Infections and neurological disorders; Hematological and lymphatic system disorders; Cardiovascular adverse effects; Macular oedema.	[151,152,176]
SEW2871	S1PR1	Specifically antagonizes S1PR1, reducing immune cell infiltration in lesions.	Cardiovascular adverse effects; Macular oedema.	[151,152]
JTE013	S1PR2	Blocks S1P-induced proliferation of endometriotic stromal cells.	–	[77]
Targeting amino acid metabolim				
1-MT	IDO1	Inhibition of IDO1 in endometriotic cells downregulates COX-2 and MMP-9, thereby suppressing cell proliferation, adhesion, and invasion.	–	[89]
1-MT	IDO1	Reduces Treg cell differentiation and improves their immunosuppressive function by inhibiting IDO1 activity.	–	[91]

Abbreviations: DCA, Dichloroacetate; PDK1/3, pyruvate dehydrogenase kinase 1/3; PDH, pyruvate dehydrogenase; LDHA, lactate dehydrogenase A; PFKFB3/4, 6-phospho-fructo-2-kinase/fructose-2,6-bisphosphatase 3/4; KRIBB11, N2–(1H-indazole-5-yl)-N6-methyl-3-nitropyridine-2,6-diamine; HSF1, heat shock factor 1; 5MPN, 5-(n-(8-methoxy-4-quinolyl)amino)pentyl nitrate; IOX1, 5-Carboxy-8-hydroxyquinoline; ALKBH5, alkylation repair homolog protein 5; HK2, hexokinase 2; PIM2, proviral insertion in murine lymphomas 2; PKM2, pyruvate kinase M2; PAK5, p21-activated kinase 5; AURKA, aurora kinase A; CHIP, U-box containing protein 1; HMGB1, high mobility group box 1; GLUTs, glucose transporters; MCTs, monocarboxylate transporters; SPHK1, sphingosine kinase 1; S1P, sphingosine-1-phosphate; FTY720, fingolimod; S1PR1/2, sphingosine-1-phosphate receptor 1/2; 1-MT, 1-methyl-DL-tryptophan; IDO1, indoleamine 2,3-dioxygenase 1.

targeting this pathway include SPHK inhibitors, S1P monoclonal antibodies, and S1PR modulators. The SPHK1 inhibitor SKI-5C reduces angiogenesis and lesion growth without affecting ovarian vasculature, suggesting value in postoperative recurrence prevention [74].

Furthermore, S1P-neutralizing antibodies block proliferation and angiogenic signaling [150] and may be combined with non-steroidal anti-inflammatory drugs to counteract macrophage-driven inflammation [76] Fingolimod, an S1PR functional antago-

Table 3
Clinical trials targeting metabolic pathways in endometriosis.

Metabolic	Drug	Primary target	Intervention	Primary objective	Status	Phase	NCT number
Glycolysis	DCA	PDK1	Oral DCA capsules: 6.25 mg/kg twice daily for 6 weeks, then 12.5 mg/kg twice daily for 6 weeks	To evaluate DCA as a potential treatment for endometriosis-associated pain	Completed	Not Applicable	NCT04046081
Glycolysis	PFK158	PFKFB3	Intravenous infusion, dose-escalation study	To determine the maximum tolerated dose, safety, and pharmacokinetics	Unknown	Phase I	NCT02044861
Glycolysis	Atorvastatin + Oral Contraceptive	GLUTs & MCTs (Indirect)	Atorvastatin 20 mg daily + oral contraceptive (21 days on/7 days off) for 6 months	To assess the efficacy of combination therapy on the pain and inflammation	Unknown	Not Applicable	NCT00675779
Glycolysis	Resveratrol + Oral Contraceptive	GLUTs & MCTs (Indirect)	Oral contraceptive for 42 days + resveratrol 40 mg daily	To evaluate pelvic pain relief with combination therapy	Completed	Phase IV	NCT02475564
Lipid Metabolism	Biomarker Study	S1PR1	No drug intervention Observational study	To detect S1PR1 levels to identify endometriosis patients	Completed	Not Applicable	NCT02973854
Tryptophan Metabolism	Ad.p53 DC Vaccine in combination with 1-MT	IDO1	Adenovirus p53 DC vaccine intradermally (6 doses) + oral 1-MT daily (up to 12 cycles)	To assess safety, dosing, and efficacy in metastatic breast cancer	Completed	Phase I/II	NCT01042535

Abbreviations:DCA, Dichloroacetate; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PDK1, pyruvate dehydrogenase kinase 1; GLUTs, glucose transporters; MCTs, monocarboxylate transporters; S1PR1, sphingosine-1-phosphate receptor 1; IDO1, indoleamine 2,3-dioxygenase 1; 1-MT, 1-methyl-D-tryptophan; Ad.p53 DC Vaccine, adenovirus p53 dendritic cell vaccine.

nist approved for multiple sclerosis, reduces immune infiltration and fibrosis; however, there are possible cardiovascular and ocular side effects [72,151,152]. Currently, a new generation of more specific S1PR antagonists is under development. The S1PR1-specific inhibitor SEW2871 has demonstrated superiority over FTY720 in suppressing inflammatory factors while exhibiting a lower incidence of lymphopenia [150]. Meanwhile, the S1PR2 antagonist JTE013 can effectively block S1P-induced proliferation of endometriotic stromal cells and the secretion of IL-6 [77]. However, given the role of S1P in oocyte maturation and pregnancy [153,154] careful evaluation of reproductive safety is essential.

Targeting amino acid metabolism

IDO inhibition

As the rate-limiting enzyme of tryptophan metabolism, IDO is a promising target. 1-methyl-DL-tryptophan (1-MT), a specific inhibitor of IDO1, exerts dual therapeutic effects in EMS. On one hand, it suppresses the expression of COX-2 and MMP-9 in endometriotic cells, thereby reducing their proliferation, adhesion, and invasion [89]. On the other hand, it limits estrogen-driven Treg differentiation and restores immune surveillance. Animal studies have demonstrated that 1-MT can reduce the number and weight of ectopic lesions, effectively reversing the progression of EMS [91]. At the time of writing, Phase I and II clinical trials on 1-MT for cancer immunotherapy are ongoing [85]; it is also a promising drug for metabolic diseases [155]. However, the absorption efficiency and bioavailability of free 1-MT are limited by its poor solubility. To address this, specific, effective, and highly biocompatible nano-platform strategies are now being developed to enable precise treatment and avoid off-target effects [156]. Intrauterine devices releasing 1-MT are under consideration for localized therapy. Treatment selection should consider individual immune status.

There is significant metabolic heterogeneity among patients with EMS, meaning that a "one-size-fits-all" treatment strategy is inefficient. Future clinical trials should incorporate patient stratification based on metabolic subtypes, such as glycolysis-dominant or immune-metabolic disorder subtypes, lesion location, and fertility needs. Potent glycolytic inhibitors such as DCA may be more suitable for patients without fertility demands and with a glycolysis-dominant subtype, whereas IDO1 inhibitors could offer dual benefits for patients presenting with both infertility and abnormal tryptophan metabolism. This biomarker-driven approach is essential for enriching trial populations and demonstrating efficacy in patients most likely to benefit.

However, although targeting glucose, lipid, and amino acid metabolic pathways shows potential in EMS treatment, clinical translation faces multiple challenges. Firstly, glycolytic inhibitors risk systemic toxicity due to the central role of glucose metabolism. Secondly, while lipid metabolism-related inhibitors have anti-inflammatory and anti-angiogenic effects, they may affect ovarian function and fertility, or cause adverse reactions such as cardiovascular effects. Thirdly, amino acid metabolism inhibitors such as IDO inhibitors must be used based on individual immune status; otherwise, there may be disruption of local immune tolerance. The current landscape of these clinical investigations is summarized in Table 3. Current solutions include developing highly selective inhibitors, using nanocarriers or localized delivery to concentrate drugs at lesions, and incorporating long-term reproductive safety monitoring into clinical trials to balance efficacy with fertility preservation.

Translational roadmap

Although research on metabolic reprogramming has opened new perspectives for EMS diagnosis and treatment, its heterogeneity and the complexity of its mechanisms still present formidable challenges. The effective integration of metabolic regulatory strategies into clinical diagnostic and therapeutic frameworks is critical to driving progress in this field. The development of metabolically targeted therapies for endometriosis adheres to the classic translational paradigm: mechanism elucidation, target validation, preclinical evaluation, and clinical development. Currently, only a few metabolic-targeting drugs have entered clinical stages, mostly in early phases (I/II). The designs of clinical trials should consider patient stratification, enrolling patients based on metabolic subtypes to improve the measurement of efficacy. Optimization of

Table 4
Preclinical studies targeting metabolic pathways in endometriosis.

Target metabolite	Experimental model	Intervention	Key findings	Safety data	Ref.
Glycolysis					
PDK1/PDH axis	Human ESC	DCA in vitro	Upregulated PDK1 expression, increased lactate production, and oxygen consumption in ectopic endometrial stromal cells; reversed by DCA.	NR	[37]
PDK1/PDH axis	Human peritoneal mesothelial-stromal cell co-culture; Mouse endometriosis model	DCA in vitro; Oral DCA in vivo	Enhanced glycolysis and lactate secretion, reduced PDH activity in Endo HPMCs; DCA corrected metabolic phenotype; oral DCA reduced lactate and lesion size in mice.	NR	[139]
PDK1	12Z; THES	CS extract in vitro	• CS reduced PDK1 expression and PDHA phosphorylation, inhibited lactate production, induced apoptosis; higher toxicity in 12Z vs. THES cells.	Lower toxicity in normal cells	[141]
PDK1/3 & LDHA	12Z and THES; Mouse endometriosis model	PV extract in vitro; Oral PV in vivo	PV inhibited LDHA activity, reduced PDK1/3 expression and PDHA phosphorylation, decreased lactate production, reduced lesion number and weight in mice.	Histological examination revealed no significant toxicity.	[143]
PFKFB3	11Z and EESC; Mouse endometriosis model	PFK-015 in vitro; i.p. injection	PFKFB3 upregulated in ectopic tissues, enhanced glycolysis and cell proliferation; PFK-015 suppressed ectopic lesion growth.	No body weight difference	[23]
HSF1-PFKFB3 axis	11Z and human ESC; Mouse endometriosis model	KRIBB11 in vitro and in vivo	HSF1 upregulated PFKFB3, enhanced glycolysis, promoted proliferation and migration; KRIBB11 reduced PFKFB3 expression and lesion number, weight, and size.	NR	[25]
PFKFB4	11Z and ectopic ESC; Mouse endometriosis model	5MPN in vitro and in vivo	CHIP reduced PFKFB4 protein stability, inhibited glycolysis, regulated proliferation, migration, and invasion; 5MPN suppressed lesion formation and growth.	No body weight difference	[27]
ALKBH5-HK2 axis	Mouse endometriosis model	IOX1 i.p. injection	ALKBH5 was upregulated in ectopic endometrium, positively regulated HK2 and glycolysis; IOX1 inhibited ALKBH5 and HK2 expression, reduced lesion number and volume.	NR	[20]
PIM2-PKM2 axis	11Z and primary EESC; Mouse endometriosis model	SMI-4a in vitro and in vivo	PIM2 was upregulated in ectopic endometrium, promoting glycolysis and fibrosis; SMI-4a inhibited these effects and disease progression.	NR	[29]
PKM2	Primary ESC	Cinnamic acid in vitro	Cinnamic acid inhibited PKM2 expression, reduced cell viability, invasion, extracellular acidification rate, and oxygen consumption in EESCs.	NR	[31]
PAK5-PKM2 axis	11Z and HESC; Mouse endometriosis model	GNE2861 in vitro; i.p. injection	PAK5 was upregulated in endometriosis; knockdown or GNE2861 treatment significantly inhibited lesion formation and progression.	NR	[30]
AURKA-ERβ axis	11Z and primary ovarian EESC; Mouse endometriosis model	Treatment with AURKA inhibitor Alisertib in vitro (IC50 determined); Intraperitoneal injection (20 mg/kg, twice/week for 1 month) in vivo	AURKA upregulated in endometriotic tissues, promoted progression via ERβ upregulation; Alisertib showed therapeutic potential.	Not reported	[147]
CHIP-HMGB1 axis	11Z and ectopic ESC; Mouse endometriosis model	Treatment with CHIP agonist YL-109 (15 mg/kg, i.p., twice/week for 1 month)	CHIP inhibited endometriosis progression via HMGB1 degradation; YL-109 suppressed lesion growth and reduced glucose and lactate in peritoneal fluid.	Not reported	[148]
GLUTs & MCTs	Rat endometriosis model	Oral administration for 28 days: Atorvastatin 5 mg/kg, Resveratrol 40 mg/kg, or combination	Both single and combined treatments reduced ectopic endometrial tissue and angiogenesis, with the combination showing superior efficacy.	No obvious adverse reactions observed; detailed safety data not provided.	[41]
Lipid Metabolism					
S1P signaling (SPHK1)	Mouse endometriosis model	Intraperitoneal injection of SPHK1 inhibitor SKI-5C (10 mg/kg for 7, 14, or 28 days)	SKI-5C significantly reduced the formation and growth of peritoneal endometriotic lesions.	No apparent systemic toxicity or behavioral abnormalities; no effect on ovarian or uterine vascular density.	[74]
S1P signaling (S1PR)	Mouse endometriosis model	Intraperitoneal injection of S1PR modulators: FTY720 (1 mg/kg/day) or SEW2871 (0.5 mg/kg/day) for 14 days	FTY720 and SEW2871 inhibited lesion growth and reduced collagen deposition.	No significant weight changes; FTY720 reduced blood lymphocyte proportion; SEW2871 slightly increased macrophage proportion; high-dose FTY720 caused systemic toxicity.	[151]

(continued on next page)

Table 4 (*continued*)

Target metabolite	Experimental model	Intervention	Key findings	Safety data	Ref.
SphK1-S1P-S1PR axis	Human Primary ESC	Stimulation with gradient S1P; Treatment with S1PR antagonists JTE013 or VPC23019 (10 μM)	High S1P promoted ESC proliferation. JTE013 and VPC23019 inhibited this pro-proliferative effect.	Not reported	[77]
Amino Acid Metabolism					
Kynurenine Pathway (IDO1)	Human primary ESC	LPS (10 ng/ml) pretreatment followed by L-1-MT (0.05 mM, IDO1 inhibitor)	IDO1 was upregulated in eutopic and ectopic ESCs from endometriosis patients; L-1-MT inhibited IDO1 and suppressed disease progression.	NR	[89]

Abbreviations: DCA, Dichloroacetate; PDK1/3, pyruvate dehydrogenase kinase 1/3; PDH, pyruvate dehydrogenase; HPMCs, human peritoneal mesothelial-stromal cells; HSF1, heat shock factor 1; CS, Caesalpinia sappan; PV, Prunella vulgaris; EESC, endometriotic endometrial stromal cells; ESC, endometrial stromal cells; PFKFB3/4, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3/4; CHIP, carboxyl terminus of Hsp70-interacting protein; ALKBH5, alkylation repair homolog protein 5; HK2, hexokinase 2; PAK5, p21-activated kinase 5; AURKA, aurora kinase A; HMGB1, high mobility group box 1; GLUTs, glucose transporters; MCTs, monocarboxylate transporters; S1P, sphingosine-1-phosphate; SPHK1, sphingosine kinase 1; S1PR, sphingosine-1-phosphate receptor; FTY720, fingolimod; IDO1, indoleamine 2,3-dioxygenase 1; L-1-MT, L-1-methyl-tryptophan; NR, Not reported.

administration strategies, such as local delivery, combination therapy, and sequential therapy, holds promise for development and should be systematically evaluated in clinical settings. In the future, by integrating multi-omics screening, real-time metabolic imaging, and computational models, it may be possible to achieve early diagnosis, dynamic monitoring, and personalized metabolic therapy. Although the translation of metabolic targeted therapy in EMS remains in its early stages, the path is becoming clearer and holds promise for translating this therapeutic strategy into clinical benefits. Preclinical studies using cellular and animal models have identified key nodes in glycolysis, lipid metabolism, and amino acid metabolism in EMS and screened many promising inhibitors. These preclinical findings are comprehensively summarized in Table 4. However, the metabolic heterogeneity of EMS and the complexity of the lesion microenvironment place higher demands on the models. Future efforts should focus on developing patient-derived organoids and humanized immune system mouse models to better simulate human metabolic and immune interactions. Furthermore, integrative multi-omics analysis should be used to identify biomarkers predictive of treatment efficacy and for patient stratification in clinical studies.

Challenges and future directions

Metabolic reprogramming plays a central role in EMS pathogenesis. Current studies largely focus on single metabolic pathways or specific cell types, impeding comprehensive elucidation of the complex synergistic (or antagonistic) interactions of glucose, lipid, and amino acid metabolism. To advance mechanistic understanding, it is necessary to integrate spatial metabolomics with single-cell transcriptomics to construct spatiotemporal metabolic maps, and to develop organoid co-culture models mimicking the in vivo microenvironment. These approaches may help unravel the intricate metabolic interactions between cells, as well as between cells and the extracellular matrix within the tissue microenvironment. This would deepen the current understanding of EMS development and its impairment of oocyte quality.

At the therapeutic level, there remain major challenges to targeting metabolic pathways. Ectopic endometrial cells exhibit high metabolic flexibility and heterogeneity, which narrows the therapeutic window due to substantial overlap with normal cell metabolism. The complex interactions of metabolic drugs within the microenvironment further complicate therapeutic outcomes. Hormonal therapy, as the first-line treatment for endometriosis, exerts its effects by systematically altering the levels of sex hormones. However, these interventions are potent metabolic modulators, and their impacts constitute a non-negligible consideration in treatment decision-making. Long-term use of oral contraceptives can alter the plasma lipid profile and predispose to insulin resistance [157,158]. This may, to some extent, exacerbate endometriosis-associated changes in lipid metabolism and provide a favorable metabolic environment for lesions, potentially increasing the burden for patients with pre-existing dyslipidemia, highlighting the importance of baseline metabolic assessment. Gonadotropin-releasing hormone agonists induce an acute hypoestrogenic state, which can cause bone metabolism abnormalities in the short term. Although "add-back therapy" can alleviate complications, the interaction between this artificially reconstructed hormonal milieu and the locally abnormal metabolism of lesions remains unknown. Cellular metabolic plasticity also represents a major obstacle to treatment, as it allows cells to rapidly adapt under therapeutic pressure by switching to alternative metabolic routes. This enables cells maintain biosynthesis, redox homeostasis, and energy supply when key metabolic nodes are inhibited, thus weakening the effectiveness of targeted therapy. Combination strategies integrating metabolic inhibitors with immunotherapy, anti-angiogenic drugs, or traditional hormonal therapies hold promise. Through synergistic suppression of lesion progression via multiple pathways, such combinations may enhance efficacy, reduce drug dosages, and delay resistance.

Specific locations of endometrial lesions may be amenable to local drug delivery to increase concentrations and reduce side effects. For peritoneal lesions, intraperitoneal injection is a feasible approach; for lesions associated with adenomyosis or prone to recurrence, intrauterine devices could be adapted to deliver applications that continuously release IDO inhibitors. For localized, deep-infiltrating lesions visible during surgery, intra-lesional injection during the procedure can be performed to eradicate residual lesions and prevent recurrence.

Nanoparticle delivery systems hold promise for addressing the narrow therapeutic window. By designing nanoparticles or co-delivery systems that trigger release under EMS microenvironment-specific conditions such as low pH, high ROS, or the presence of specific enzymes, and co-loading two metabolic inhibitors with synergistic effects, such as glycolysis and glutaminase inhibitors, it is possible to cut off both carbon and nitrogen sources for ectopic cells, with the aims of achieving synergistic effects and minimizing systemic side effects. In the future, patient stratification by metabolomic subtypes could guide medication combinations to prevent activation of compensatory pathways. Real-time metabolic imaging can detect dynamic changes in cellular metabolic states under therapeutic interventions, providing a basis for designing personalized sequential treatment regimens.

Metabolomics provides a direct reflection of real-time biochemical states and serves as a critical bridge between genotype and phenotype. Comparative analysis of metabolic profiles under

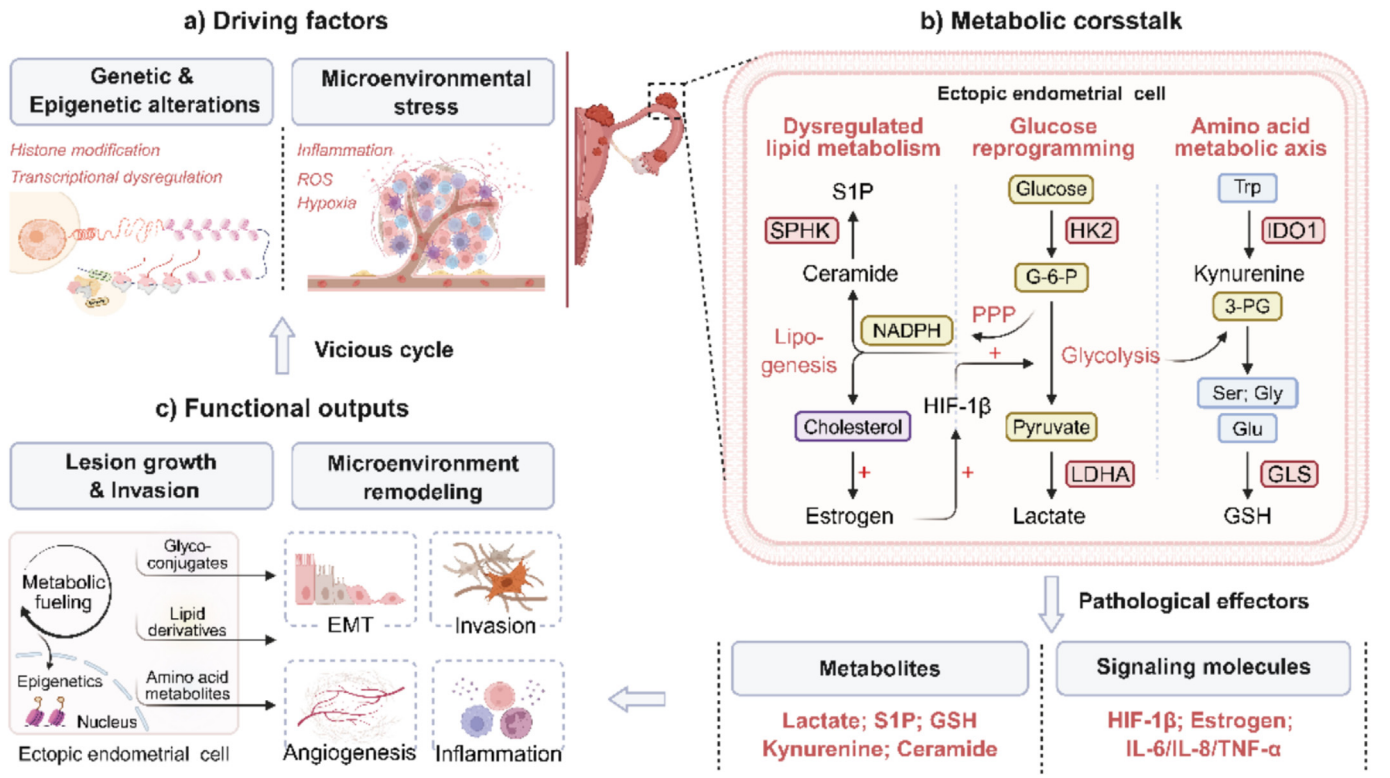

Fig. 4. An integrative model of metabolic reprogramming in EMS. The pathogenic progression of EMS is initiated by convergent factors, encompassing genetic/epigenetic alterations, a stressed microenvironment, and hormonal dysregulation. Together, these inputs remodel the core metabolic network in ectopic endometrial cells, amplifying glucose flux, dysregulating lipid metabolism, and reprogramming amino acid metabolism. This metabolic rewiring results in the synthesis of a spectrum of pathological metabolites and signaling molecules, which subsequently fuel key disease-promoting processes, reinforcing a self-perpetuating vicious cycle that drives the persistence of lesions and contributes to infertility. 3-PG, 3-phosphoglycerate; G-6-P, glucose-6-phosphate; GLS, glutaminase; Glu, glutamate; Gly, glycine; GSH, glutathione; HIF-1β, hypoxia-inducible factor 1β; HK2, hexokinase 2; IDO1, indoleamine 2,3-dioxygenase 1; IL-6, interleukin-6; LDHA, lactate dehydrogenase A; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); PPP, pentose phosphate pathway; S1P, sphingosine-1-phosphate; Ser, serine; SPHK, sphingosine kinase; TNF-α, tumor necrosis factor-alpha; Trp, tryptophan. The image was created with BioRender.com under a paid license.

healthy versus disease conditions can identify EMS-specific metabolic biomarkers, which may aid early diagnosis and prognosis evaluation. Currently, oocyte and embryo quality assessment predominantly relies on morphology. In-depth metabolomic profiling of the FF, which captures the metabolic features of the follicular microenvironment may enable the identification of biomarkers for assessing oocyte quality and embryonic developmental potential. This could ultimately improve clinical outcomes of oocyte cryopreservation in assisted reproductive technology.

Conclusions

EMS is an estrogen-dependent chronic disorder characterized by metabolic reprogramming. Ectopic endometrial cells remodel glucose, lipid, and amino acid metabolic pathways in response to adverse microenvironments (hypoxia, immune stress, oxidative stress), exhibiting malignant phenotypes including sustained proliferation, enhanced angiogenesis, and increased invasiveness. These cells actively contribute to remodeling of the disease microenvironment, facilitate immune evasion, and drive disease progression. Simultaneously, EMS disrupts the follicular microenvironment, inducing metabolic reprogramming in granulosa cells. This decreases oocyte quality and embryonic developmental potential, representing a key mechanism underlying the associated infertility. Collectively, metabolic reprogramming functions not only as an adaptive strategy for cells under pathological stress, but also as a central hub promoting disease malignancy and infertility (Fig. 4). Targeted interventions against specific metabolic pathways may overcome the limitations of conventional hormonal therapies, offering novel strategies and potential therapeutic targets for precision treatment.

Author contributions

DL, YL, and ZJ designed and conceived the review. CG, XN, ZG and JJ wrote the manuscript. MY, JL, WD, DZ, and ZN generated the figures. All the authors approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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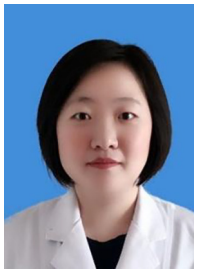

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Xinni Na is a clinician and an MD in the Department of Obstetrics and Gynecology at China Medical University. She has published 5 SCI papers in the fields of obstetrics, gynecology, and reproductive medicine. Her current research focuses on the impact of metabolites such as lactate on pregnancy outcomes. In this review, she wrote the original draft and generated the figures.

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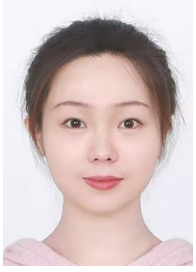

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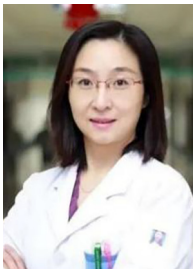
Zhongxiu Jiang is a clinician in the Oncology Department of Shengjing Hospital, China Medical University. She has published 7 SCI papers in the field of cancer pathogenesis and treatment. She is currently researching the metabolic characteristics and metabolic therapies of cancer. In this article, she provided ideas and insights from the perspective of tumor metabolic reprogramming.



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