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REVIEW

Metabolic Reprogramming Shapes the Progression and Therapeutic Landscape of Ovarian Cancer

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Abstract: Ovarian cancer (OC) remains one of the most lethal gynecologic malignancies due to its asymptomatic progression, frequent late-stage diagnosis, and high rates of chemoresistance and recurrence. Beyond genetic alterations, recent studies highlight the central role of metabolic reprogramming in driving OC initiation, progression, and therapy resistance. OC cells exhibit dynamic metabolic reprogramming, enabling dynamic shifts between glycolysis and oxidative phosphorylation depending on environmental conditions and treatment pressures. In this review, we synthesize current understanding of key metabolic pathways altered in ovarian tumors, including enhanced aerobic glycolysis, glutamine addiction, dysregulated lipid metabolism, and mitochondrial adaptations. These metabolic shifts support rapid proliferation, redox homeostasis, immune evasion, and metastatic potential. We also explore how the metabolic landscape of OC is shaped by interactions with the tumor microenvironment, particularly through crosstalk with immune cells, cancer-associated fibroblasts, and adipocytes. Importantly, metabolic adaptations have been implicated in the emergence of cancer stem-like cells and in the development of resistance to platinum-based chemotherapy and PARP inhibitors. We also further discuss emerging therapeutic strategies targeting metabolic vulnerabilities, as well as combinatorial approaches integrating metabolic therapy with immunotherapy and DNA damage repair inhibition. Finally, we highlight how advances in metabolomics and spatial profiling are improving our ability to map metabolic heterogeneity and guide precision therapies in OC. This review underscores metabolic plasticity as a promising therapeutic vulnerability for overcoming drug resistance and improving outcomes in OC patients.
Keywords: ovarian cancer, metabolic reprogramming, chemoresistance, tumor microenvironment, cancer stem cells

Introduction

Ovarian cancer (OC) remains one of the deadliest gynecologic malignancies in cancer-related deaths among women globally.[1] A recent study analyzing trends from 1990 to 2019 projected that by 2049, the age-standardized incidence and mortality rates of OC r in China could reach 8.95 and 4.03 per 100,000 population, respectively, highlighting an urgent need for improved early detection and preventive strategies.[2,3] The most prevalent and aggressive subtype is high-grade serous ovarian carcinoma (HGSOC), accounting for approximately 70% of epithelial OC cases.[4] HGSOC typically originates from the distal fallopian tube epithelium and is characterized by extensive genomic instability, TP53 mutations, and frequent homologous recombination deficiency.[5,6] Despite initial responsiveness to platinum-based chemotherapy, most patients experience relapse and ultimately develop drug-resistant disease.[7–9] The five-year survival rate for advanced-stage HGSOC remains below 30%, underscoring the urgent need for improved therapeutic strategies.[10–12]

Recently, a paradigm shifts in our understanding of OC biology with more and more recognition that metabolic reprogramming is not merely a consequence of malignancy but a fundamental driver of tumor progression, immune evasion, and therapeutic resistance.[13,14] OC cells undergo profound alterations in energy metabolism to sustain proliferation, survive under hypoxic conditions, and adapt to fluctuations in nutrient availability, which is consistent with many other tumors.[15,16] This metabolic plasticity characterized by increased glycolytic activity, glutamine dependence, mitochondrial metabolic reprogramming, and alterations in lipid metabolism, facilitating their adaptation to the tumor

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microenvironment.[13] Notably, metabolic phenotypes in OC exhibit significant heterogeneity across tumor subtypes and dynamically evolve in response to microenvironmental stresses and therapeutic interventions.[17]

OC exhibits a distinct metastatic behavior characterized by transcoelomic dissemination within the peritoneal cavity, accompanied by intricate metabolic interactions with components of the tumor microenvironment, including omental adipocytes, mesothelial cells, and constituents of ascitic fluid.[18] This microenvironmental context creates selective pressures that further shape tumor metabolism, facilitating immune suppression, stem-like phenotypes, and resistance to chemotherapy.[13,14,18] Moreover, cancer stem cells (CSCs) in ovarian tumors display distinct metabolic features, including reliance on oxidative phosphorylation and enhanced antioxidant capacity, which enable them to persist following treatment and initiate recurrence.[2,19]

Based on these findings, targeting tumor metabolism has emerged as a promising therapeutic strategy. Several metabolic enzymes such as hexokinase 2 (HK2), lactate dehydrogenase A (LDHA), glutaminase (GLS1), and fatty acid synthase (FASN) are overexpressed in OC and have been implicated in poor prognosis and resistance phenotypes.[20] Inhibitors of these enzymes are currently under preclinical and clinical investigation, either as monotherapies or in combination with existing chemotherapies and immune checkpoint inhibitors.[21–23] Furthermore, the integration of metabolomic profiling, isotope tracing, and single-cell analyses is enabling unprecedented resolution of metabolic heterogeneity in ovarian tumors.[24]

This review provides a comprehensive overview of how metabolic reprogramming shapes OC progression and impacts therapeutic response. Hallmark metabolic alterations observed in ovarian tumors are first delineated, including dysregulated glycolysis, mitochondrial dysfunction, and aberrant amino acid and lipid metabolism. The interplay between metabolic pathways and the tumor microenvironment, immune landscape, and metastatic niche is then examined, with particular emphasis on the contribution of metabolism to drug resistance, cancer stemness, and disease relapse. Emerging therapeutic strategies that target metabolic vulnerabilities are evaluated, encompassing both monotherapies and combination regimens designed to overcome resistance mechanisms. Recent technological advances are discussed for their potential to accelerate the identification of predictive biomarkers and novel therapeutic targets. Current challenges and future directions in translating metabolic research into precision oncology for OC are also outlined. By synthesizing recent advances in tumor metabolism with the evolving therapeutic landscape, this review highlights the critical role of bioenergetic plasticity in shaping treatment outcomes and emphasizes the necessity of elucidating metabolic dependencies to inform the development of more effective and personalized therapeutic strategies. The interrelated domains of metabolic reprogramming, tumor microenvironmental dynamics, therapeutic resistance, and emerging metabolic-targeted interventions in OC are illustrated in Figure 1.

Hallmarks of Metabolic Reprogramming in OC

Metabolic reprogramming is now recognized as a fundamental hallmark of cancer, conferring proliferative, survival, and adaptive advantages to tumor cells.[25] This metabolic flexibility also supports disease progression, immune evasion, and therapeutic resistance, particularly in the context of the hypoxic, nutrient-deprived tumor microenvironment in OC.[14] Metabolic reprogramming in OC is orchestrated through four interrelated axes encompassing glycolysis, mitochondrial dynamics coupled with oxidative phosphorylation, amino acid metabolism, and lipid metabolism, which together drive the acquisition and maintenance of malignant phenotypes.[20,26]

Warburg Effect and Aerobic Glycolysis

One of the earliest and most consistent metabolic features observed in OC is enhanced aerobic glycolysis, commonly known as the Warburg effect. Even in the presence of oxygen, cancer cells preferentially convert glucose to lactate, which fuels biomass production and acidifies the tumor microenvironment, promoting invasion and immune escape.[20,26] This shift is driven by the upregulation of key glycolytic enzymes, including hexokinase 2 (HK2), phosphofructokinase B3 (PFKFB3), and lactate dehydrogenase A (LDHA).[26–28] HK2 promotes glucose phosphorylation and mitochondrial binding, facilitating efficient ATP production, while PFKFB3 boosts glycolytic flux under growth-promoting conditions.[29] LDHA converts pyruvate into lactate, maintaining NAD+ regeneration and allowing continuous glycolysis.[30]

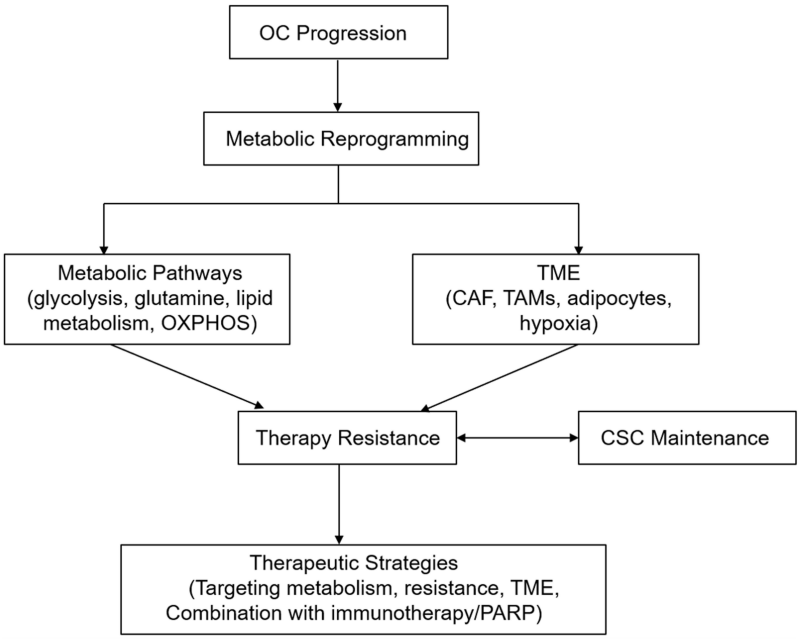

Figure 1 Schematic overview of metabolic reprogramming, TME, therapy resistance, and therapeutic strategies in OC.

These enzymatic changes are regulated by transcription factors such as hypoxia-inducible factor-1α (HIF-1α) and c-MYC, both of which are frequently overexpressed in OC.[31,32] Under hypoxic conditions, HIF-1α upregulates the expression of glycolytic genes and glucose transporters (GLUT1), facilitating metabolic adaptation.[33] Simultaneously, MYC enhances the expression of LDHA and PFK1 and promotes glutamine metabolism, linking glycolysis to anabolic biosynthesis.[34,35]

Notably, elevated glycolytic activity has been associated with platinum resistance and poor prognosis in OC patients.[26,36,37] Metabolic inhibitors targeting glycolysis, such as 2-deoxy-D-glucose (2-DG) and PFKFB3 inhibitors, are under investigation as potential sensitizers to chemotherapy.[36] While increased aerobic glycolysis has been associated with aggressive tumor behavior and poor prognosis in several studies, other reports have shown inconsistent correlations with clinical outcomes in OC. These discrepancies may reflect differences in tumor subtype, metabolic plasticity, and methodological variability across studies. Further clinical and translational investigations are needed to clarify the prognostic significance of glycolytic activity in OC.

Mitochondrial Dynamics and Oxidative Phosphorylation (OXPHOS)

While glycolysis dominates in rapidly proliferating tumor cells, recent studies suggest that mitochondrial OXPHOS is crucial for sustaining survival in subpopulations of OC cells, particularly CSCs and drug-resistant clones.[38] These cells exhibit a hybrid metabolic phenotype, characterized by the ability to switch between glycolysis and OXPHOS depending on nutrient availability and oxidative stress.[19]

Recently, enhanced oxidative phosphorylation activity has been found to be associated with increased mitochondrial mass, elevated membrane potential, and augmented respiratory capacity in platinum-resistant HGSOC models.[39] This phenotype enables more efficient ATP generation and supports the high energy demands of drug-resistant cells.[39] In addition, mitochondrial biogenesis, fusion, and fission events are tightly regulated during tumor progression. Proteins such as DRP1 and OPA1 coordinate these processes, and their dysregulation contributes to metabolic imbalance and apoptotic resistance.[40]

Importantly, OXPHOS-dependent CSCs demonstrate resistance to conventional therapies and contribute to recurrence after treatment cessation.[19] Therapeutic strategies such as metformin, IACS-010759, and CPI-613 have shown promise in targeting OXPHOS and reducing CSC viability in preclinical OC models.[41–44] Dual targeting of glycolysis and OXPHOS may offer synergistic benefits by limiting metabolic compensation.[45]

Glutamine Metabolism and Amino Acid Dependencies

Beyond glucose metabolism, OC cells exhibit high dependency on glutamine as a carbon and nitrogen source to fuel the TCA cycle, produce nucleotides, and maintain redox balance.[46] Glutaminase enzymes, particularly GLS1 and GLS2, catalyze the conversion of glutamine to glutamate, a critical step for anaplerosis and biosynthesis.[47,48] Overexpression of GLS1 has been observed in HGSOC and is correlated with increased aggressiveness and chemoresistance.[49]

Additionally, serine and glycine metabolism, which are intimately associated with the one-carbon metabolic network, play essential roles in supporting nucleotide biosynthesis, regulating methylation reactions, and maintaining redox homeostasis through the generation of NADPH and glutathione.[50,51] Key enzymes such as phosphoglycerate dehydrogenase (PHGDH) and serine hydroxymethyltransferase 2 (SHMT2) are frequently upregulated in OC and function as metabolic checkpoints that sustain the rapid proliferation of tumor cells.[20,52] Therapeutic strategies targeting these enzymes are under investigation, particularly in tumors characterized by elevated serine and glycine flux.[53]

Amino acid metabolism also intersects with immune evasion. For instance, depletion of tryptophan by indoleamine 2,3-dioxygenase (IDO1) contributes to T cell anergy and regulatory T cell expansion in the OC microenvironment.[54,55]

Although glutaminase inhibitors have demonstrated efficacy in preclinical OC models, their clinical performance has been variable. This suggests that glutamine dependency may differ across OC subtypes and could be influenced by tumor microenvironmental factors. Stratification based on molecular or metabolic biomarkers may be essential to identify responsive patient populations.

Lipid Metabolism Reprogramming

OC progression is further supported by profound reprogramming of lipid metabolism. Tumor cells increase fatty acid uptake, synthesis, and oxidation to meet demands for membrane biosynthesis, energy generation, and signaling lipid production.[56] CD36, a fatty acid translocase, facilitates lipid uptake from the surrounding adipocyte-rich omental environment, particularly in metastatic OC.[57] Concurrently, de novo fatty acid synthesis is enhanced through the upregulation of FASN, which is associated with tumor aggressiveness and poor prognosis.[58,59]

Fatty acid oxidation (FAO) via carnitine palmitoyltransferase 1A (CPT1A) enables mitochondrial energy production and supports stemness, chemoresistance, and survival under metabolic stress.[60,61] Inhibition of CPT1A has been shown to sensitize OC cells to paclitaxel and reduce tumor growth in vivo.[62]

Lipid reprogramming also contributes to immune evasion. Accumulation of lipid droplets and oxidized lipids in dendritic cells and macrophages impairs antigen presentation and promotes an immunosuppressive phenotype.[63,64] Therapies targeting lipid metabolic enzymes, including FASN inhibitors and CPT1A blockers, are currently being explored for their capacity to reverse metabolic immunosuppression and improve treatment outcomes.[56,65] A summary of the major metabolic pathways reprogrammed in ovarian cancer is provided in Table 1.

Table 1 Key Metabolic Pathways Reprogrammed in OC

Metabolic Pathway	Major Changes in OC	Key Molecules	Associated Effects	References
Glycolysis (Warburg Effect)	Increased aerobic glycolysis even in oxygen-rich conditions; conversion of glucose to lactate	HK2, PFKFB3, LDHA, GLUT1	Promotes biomass production, immune escape, platinum resistance	[20,26–37]
Mitochondrial Dynamics and OXPHOS	Enhanced OXPHOS activity, increased mitochondrial mass and respiratory capacity	DRP1, OPA1, Complex I	Supports CSC survival, chemoresistance, energy production under stress	[19,38–45]
Glutamine Metabolism and Amino Acid Dependencies	Increased glutamine addiction; reliance on serine/glycine metabolism for biosynthesis and redox control	GLS1, GLS2, PHGDH, SHMT2, IDO1	Fuels TCA cycle, supports nucleotide synthesis, promotes immune evasion	[20,46–55]
Lipid Metabolism Reprogramming	Enhanced fatty acid uptake, synthesis, and oxidation	CD36, FASN, CPT1A	Supports metastasis, chemoresistance, stemness, and immune suppression	[56–65]

Metabolic Adaptations and Tumor Microenvironment (TME) Interactions

TME in OC is a dynamic and metabolically heterogeneous niche comprising not only cancer cells but also immune cells, stromal components, adipocytes, fibroblasts, and endothelial cells.[66] Metabolic reprogramming within tumor cells is both a driver and a consequence of the evolving TME, fostering a reciprocal relationship that supports immune evasion, metastatic dissemination, and therapy resistance.[15,67] Understanding how OC metabolism interfaces with the TME is critical for identifying new therapeutic targets and predicting treatment outcomes.

Crosstalk Between Tumor Metabolism and Immune Cells

One of the most prominent metabolic byproducts in the ovarian TME is lactate, generated through enhanced glycolytic activity. Excess lactate accumulation leads to acidification of the local environment and contributes to T cell exhaustion and dysfunction.[68] High lactate levels inhibit T cell proliferation, cytokine secretion, and cytotoxic function by impairing glycolysis-dependent energy generation.[69] Furthermore, lactate directly induces the expression of immune checkpoint molecules such as PD-L1 on both tumor and stromal cells, thereby dampening antitumor immunity.[70,71]

Tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) undergo significant metabolic adaptation within the ovarian tumor microenvironment. In response to lactate accumulation and hypoxia, TAMs are skewed toward an M2-like phenotype characterized by enhanced angiogenesis, extracellular matrix remodeling, and immunosuppressive activity.[72] Lactate-stimulated TAMs upregulate arginase-1 and vascular endothelial growth factor (VEGF), while concomitantly suppressing pro-inflammatory signaling pathways.[73] Tregs preferentially survive and maintain suppressive functions in low-glucose, high-lactate conditions by relying on oxidative phosphorylation as a primary energy source.[74] Similarly, MDSCs promote immune evasion by depleting key amino acids, particularly arginine and tryptophan, thereby impairing T cell activation and effector responses.[75]

Recent findings indicate that the metabolic flexibility of immunosuppressive cell subsets closely parallels that of tumor cells, enabling their adaptation to nutrient deprivation and oxidative stress within the tumor microenvironment.[15] Therapeutic interventions that selectively disrupt key metabolic pathways in these cells, such as inhibition of monocarboxylate transporters (MCTs) responsible for lactate export or blockade of indoleamine 2,3-dioxygenase 1 (IDO1)-mediated tryptophan catabolism, are being actively explored as strategies to restore antitumor immune responses.[76,77]

Stromal Support and Metabolic Symbiosis

Beyond immune cells, stromal components play a critical role in shaping the metabolic landscape of ovarian tumors. One unique aspect of OC metastasis is its preferential spread to the omentum, a fat-rich environment that serves as both a physical niche and a metabolic reservoir.[78] Adipocytes in the omentum transfer free fatty acids (FFAs) to OC cells through a CD36-mediated mechanism, fueling β-oxidation and supporting metastatic outgrowth.[57] This lipid transfer not only enhances ATP production but also provides building blocks for membrane synthesis and signaling lipids that promote invasion.[79]

Cancer-associated fibroblasts (CAFs), a major stromal component of the tumor microenvironment, actively contribute to metabolic reprogramming through both nutrient competition and metabolic coupling with cancer cells. CAFs engage in aerobic glycolysis and secrete lactate, which is subsequently taken up by tumor cells and converted into pyruvate to fuel mitochondrial oxidative metabolism, a process referred to as the reverse Warburg effect.[80] In addition to lactate production, CAFs secrete amino acids and cytokines such as interleukin-6 (IL-6), thereby supporting tumor proliferation and modulating the function of immune cells.[81,82]

Recent single-cell and co-culture studies have confirmed that OC cells exhibit distinct metabolic preferences depending on their proximity to CAFs or adipocytes, highlighting the spatial heterogeneity of metabolic dependencies.[83] Targeting stromal–tumor metabolic interactions, such as disrupting CD36-mediated lipid uptake or modulating fibroblast metabolism, has demonstrated preclinical efficacy in reducing metastatic burden.[57,84]

Hypoxia and Metabolic Heterogeneity

Hypoxia is a hallmark of the ovarian tumor microenvironment and exerts profound effects on cellular metabolism. Under low oxygen tension, stabilization of hypoxia-inducible factor-1α (HIF-1α) orchestrates a transcriptional program that

enhances glycolytic flux by upregulating genes such as GLUT1, HK2, and PFKFB3.[85] Concurrently, HIF-1α suppresses mitochondrial OXPHOS to reduce reactive oxygen species (ROS) accumulation.[86] Notably, hypoxia-induced metabolic rewiring not only supports tumor cell survival but also promotes immune evasion and metastatic dissemination by modulating the tumor microenvironment.[87] These adaptive responses create a heterogeneous metabolic landscape that underpins OC progression.

Metabolic Drivers of Drug Resistance and Disease Progression

Despite initial responsiveness to platinum-based chemotherapy, most patients with advanced OC eventually develop drug resistance, leading to recurrence and treatment failure.[8] Accumulating evidence indicates that metabolic rewiring is a central driver of chemoresistance and disease progression. The ability of OC cells to dynamically shift their metabolic phenotypes in response to therapeutic pressure underpins their survival, adaptation, and metastatic potential.[15] Key mechanisms include enhanced mitochondrial OXPHOS, altered glycolysis and transporter activity, metabolic reprogramming in CSCs, and plasticity in metastatic niches.

Chemoresistance and Metabolic Rewiring

Resistance to platinum-based chemotherapy remains a major obstacle in the management of OC. Emerging evidence indicates that metabolic reprogramming, particularly the upregulation of mitochondrial OXPHOS, is a critical driver of chemoresistance.[39] In resistant cells, enhanced mitochondrial biogenesis and elevated respiratory capacity enable efficient ATP production, fueling energy-intensive processes such as DNA repair and survival signaling. Furthermore, the acquisition of an OXPHOS-dominant phenotype confers resistance to oxidative stress and supports cell survival during chemotherapy-induced metabolic stress.[88] Therapeutic strategies targeting mitochondrial function have shown promise in sensitizing resistant cells and warrant further investigation.

Cancer Stemness and Metabolic Traits

Ovarian CSCs represent a subpopulation with enhanced tumorigenic potential, resistance to standard therapies, and a propensity to drive relapse. Unlike bulk tumor cells that predominantly rely on glycolysis, CSCs exhibit a hybrid metabolic phenotype, maintaining the ability to flexibly switch between glycolysis and OXPHOS depending on microenvironmental conditions.[89] OXPHOS dependency endows CSCs with robust antioxidant defenses and efficient ATP generation, promoting survival under stress.[38] These metabolic adaptations not only support CSC maintenance but also complicate therapeutic eradication, highlighting the need for dual metabolic targeting strategies. However, despite these insights, no standardized classification exists to define metabolic subtypes in resistant OC, which complicates patient stratification and predictive modeling. A schematic comparison of metabolic features between naïve and resistant OC cells is summarized in Figure 2.

Metabolic Plasticity in Metastasis

Metastasis in OC primarily occurs via transcoelomic dissemination, wherein cancer cells detach from the primary tumor and spread across the peritoneal cavity to seed distant sites such as the omentum and mesentery.[90] These metastatic processes are tightly linked to metabolic plasticity, enabling cells to adapt to diverse environmental cues and colonize lipid-rich secondary niches.[91]

The omental microenvironment provides abundant adipocyte-derived fatty acids that are imported via CD36 and used for β-oxidation in metastatic cells.[57,92] This lipid-rich milieu promotes mitochondrial respiration, enhances energy availability, and supports epithelial-to-mesenchymal transition (EMT), facilitating invasion and colonization.[93] Inhibition of FAO enzymes or CD36 significantly impairs peritoneal metastasis in murine models.[57,92]

Metabolic changes also coincide with EMT, a cellular program that promotes dissemination and stemness. During EMT, cells downregulate epithelial markers such as E-cadherin and upregulate mesenchymal genes like ZEB1 and SNAIL, alongside shifts toward increased OXPHOS and redox buffering capacity.[94,95] EMT-associated transcription factors have been shown to directly regulate metabolic enzymes, reinforcing a feedback loop between metabolic state and invasive behavior.[96]

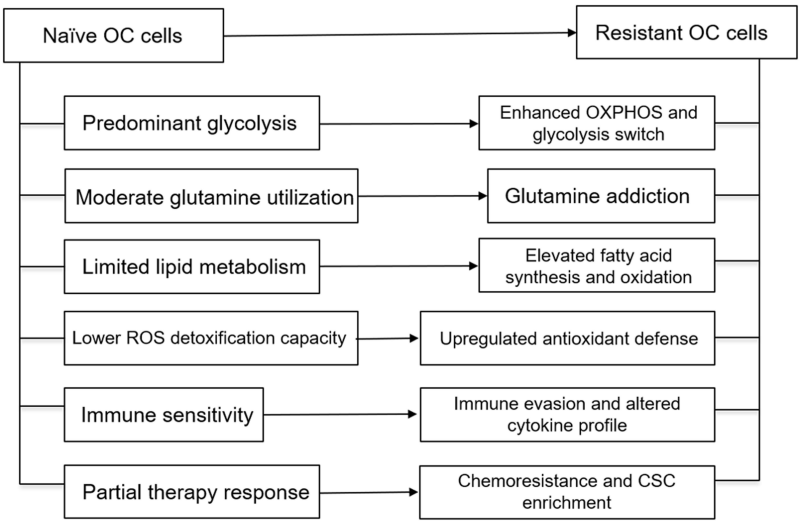

Figure 2 The comparison of the metabolic features of naïve and resistant ovarian cancer cells. Naïve cells predominantly rely on glycolysis and exhibit lower mitochondrial activity and redox capacity. In contrast, resistant cells display enhanced oxidative phosphorylation, increased lipid utilization, and elevated antioxidant defenses. These adaptations support survival under therapeutic stress and contribute to cancer stem-like properties and immune evasion.

Importantly, mesenchymal-like OC cells demonstrate resistance to anoikis, a form of apoptosis triggered by cell detachment from the extracellular matrix, as well as increased resilience to oxidative stress, facilitating their survival within the peritoneal fluid.[97] These cells are further characterized by the acquisition of stem-like properties, including enhanced capabilities for sphere formation, elevated resistance to chemotherapy, and an increased potential for metastatic seeding.[98]

The convergence of metabolic reprogramming, EMT transition, and microenvironmental adaptation forms a fundamental axis driving OC progression. Targeted therapeutic approaches aimed at disrupting this axis, including inhibition of lipid metabolic pathways, suppression of mitochondrial function, or blockade of EMT-associated transcriptional regulators, offer promising strategies for preventing metastatic dissemination and disease recurrence.[38,99]

Therapeutic Targeting of Metabolic Vulnerabilities

Metabolic reprogramming in OC not only supports malignant growth and therapy resistance but also presents novel vulnerabilities that can be therapeutically exploited. Recent advances have led to the development of targeted inhibitors against key metabolic pathways, as well as strategies that integrate metabolism with DNA repair, redox regulation, and immune modulation. This section summarizes emerging therapeutic approaches aimed at disrupting cancer-specific metabolic dependencies.

Inhibitors Targeting Key Metabolic Enzymes and Pathways

The glycolytic inhibitor 2-deoxyglucose (2-DG) sensitizes OC cells to apoptosis by suppressing glucose metabolism and activates p38 MAPK and JNK signaling pathways, thereby promoting apoptosis and inhibiting tumor progression in OC cells.[100] PFK158, inhibitor of PFKFB3, has been shown to impair homologous recombination repair by disrupting RPA3-mediated DNA damage response, thereby sensitizing OC cells to PARP inhibitors and illustrating the therapeutic potential of targeting glycolytic vulnerabilities to overcome drug resistance.[101]

OXPHOS dependency in chemoresistant and stem-like OC cells have spurred interest in mitochondrial inhibitors.[19] IACS-010759, a complex I inhibitor, disrupts electron transport chain function and selectively kills OXPHOS-reliant cells.[102] Metformin, a widely used antidiabetic drug, has been repurposed to inhibit complex I and AMPK activation in OC, reducing tumor burden and CSC activity in combination with platinum therapy.[42,103] The mitochondrial inhibitor CPI-613 targets pyruvate dehydrogenase and α-ketoglutarate dehydrogenase to suppress OXPHOS, induce mitochondrial collapse, and enhance chemotherapy sensitivity in chemoresistant OC cells.[44]

Upregulation of glutamine metabolism is a characteristic feature of aggressive ovarian tumors. The glutaminase 1 (GLS1) inhibitor CB-839, also known as telaglenastat, disrupts glutaminolysis and compromises redox homeostasis, thereby suppressing tumor proliferation and enhancing the sensitivity of OC cells to chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors.[104] Ongoing clinical trials are investigating the efficacy of CB-839 in combination regimens for the treatment of advanced OC.[105]

Targeting lipid synthesis and oxidation is particularly relevant in metastatic OC. FASN inhibitors such as TVB-2640 have shown antiproliferative effects and enhanced chemosensitivity in vivo.[106,107] Dysregulation of lipid synthesis and oxidation, characterized by upregulation of CPT1A-driven fatty acid oxidation, supports the survival of paclitaxel-tolerant OC cells, and inhibition of this pathway with the FAO inhibitor ST1326 disrupts metabolic homeostasis, sensitizes tumors to chemotherapy, and prevents disease recurrence.[108]

Synthetic Lethality and Metabolic Dependencies

Combining metabolic inhibitors with other targeted therapies offers a promising synthetic lethality approach. Metabolic modulation enhances the efficacy of PARP inhibitors by increasing oxidative stress or disrupting nucleotide supply in BRCA deficient OC.[109,110] For instance, combining CB-839 with olaparib or niraparib leads to enhanced DNA damage and tumor regression in preclinical models.[111]

NAD+/NADPH imbalance is another exploitable vulnerability. OC cells rely on NADPH for antioxidant defense and biosynthesis. Inhibitors targeting NADK, G6PD, or malic enzymes (ME1/ME2) can disrupt redox homeostasis, rendering cells more susceptible to chemotherapeutic agents.[112,113] Additionally, depletion of NAD+ using NAMPT inhibitors such as FK866 impairs sirtuin function and disrupts mitochondrial integrity, further sensitizing tumor cells to stress.[114]

Immunometabolic Combination Strategies

The immunosuppressive ovarian TME is shaped by lactate accumulation, amino acid depletion, and lipid-induced dysfunction of immune cells.[13] Targeting tumor metabolism can reverse this immunosuppression and enhance immunotherapy efficacy.

Inhibition of lactate transporters such as MCT1 and MCT4 can normalize extracellular pH and restore T cell functionality. Combining lactate transporter inhibitors with immune checkpoint blockade targeting PD-1 or CTLA-4 has been shown to reactivate anti-tumor immune responses in resistant tumors.[115] Similarly, targeting indoleamine 2,3-dioxygenase 1 (IDO1), an enzyme involved in tryptophan depletion and T cell suppression, may enhance the efficacy of immunotherapies, although early clinical trials reported limited success with IDO1 inhibitors as monotherapies.[54,116,117]

Emerging strategies aim to integrate metabolic blockade with immune checkpoint inhibition and chemotherapy. For example, dual inhibition of OXPHOS and PD-L1 pathways has been shown to reprogram the immune landscape and improve overall survival in murine OC models.[115,118] Combinatorial therapeutic strategies that integrate glycolytic inhibition with immune checkpoint blockade are actively being explored to overcome tumor-induced immunosuppression and enhance antitumor efficacy. Ultimately, a deeper understanding of the metabolic dependencies that underlie immune evasion will be key to developing effective Immunometabolic therapies. An overview of representative metabolic targets, emerging inhibitors, combination strategies, and development stages currently under investigation in OC is summarized in Table 2. A schematic overview of the metabolic vulnerabilities and therapeutic targets in OC is illustrated in Figure 3, summarizing the key pathways and their corresponding inhibitors discussed in this section.

Emerging Technologies and Future Directions in Metabolic Profiling of OC

OC is characterized by pronounced metabolic heterogeneity, shaped by genetic alterations, microenvironmental pressures, and therapeutic interventions. Recent advances in technology have enabled unprecedented resolution in profiling these dynamic metabolic states. However, translating these insights into clinical strategies remains a key challenge.

Technological Advances in Metabolic Profiling

Metabolomics, the comprehensive quantification of small-molecule metabolites, has become a cornerstone for characterizing the metabolic landscape of ovarian tumors. Liquid chromatography–mass spectrometry (LC-MS/MS) platforms allow high-

Table 2 Targeted Metabolic Therapies and Combinatorial Strategies Under Investigation in OC

Targeted Pathway	Representative Inhibitor(s)	Combination Strategy	References
Glycolysis (PFKFB3, LDHA)	PFK158, 2-DG, LDHA inhibitors	With PARP inhibitors (sensitization to DNA damage)	[36,101]
Oxidative Phosphorylation (OXPHOS)	IACS-010759, CPI-613, Metformin	With platinum therapy or PD-L1 blockade	[42–44,102]
Glutamine metabolism (GLS1)	CB-839 (Telaglenastat)	With PARP inhibitors or chemotherapy	[104,105]
Lipid metabolism (FAO, FASN)	TVB-2640, ST1326	With chemotherapy (paclitaxel) or immune modulators	[46,56,65,106,108]
Redox homeostasis (NADPH, G6PD)	G6PD inhibitors, NADK inhibitors	Increase oxidative stress to sensitize tumor cells	[112,113]
Tryptophan metabolism (IDO1)	IDO1 inhibitors (eg, Epacadostat)	With immune checkpoint blockade (PD-1/PD-L1 inhibitors)	[54,116,117]

throughput profiling of tissue, plasma, and ascites samples, revealing metabolic signatures associated with treatment response and disease progression.[119] Stable isotope tracing, particularly ^{13}C-labeled glucose and glutamine, enables real-time mapping of carbon flux through glycolysis, the TCA cycle, and biosynthetic pathways in patient-derived models.[120,121] These approaches have identified metabolic signatures predictive of platinum resistance and cancer stemness in HGSOC.

Complementing bulk metabolomics, imaging-based metabolic profiling provides spatial and functional context. Hyperpolarized ^{13}C-MRI offers real-time assessment of pyruvate-to-lactate conversion, reflecting glycolytic activity in vivo.[122] Positron emission tomography (PET) using tracers like ^{18}F-FDG and ^{11}C-acetate enables non-invasive visualization of glucose and lipid metabolism in tumors.[123,124] These imaging modalities are under investigation not only for diagnosis and staging but also for monitoring metabolic therapy response.[125]

Single-cell and spatial technologies now allow deconvolution of intratumoral metabolic heterogeneity. Single-cell RNA sequencing (scRNA-seq) has uncovered distinct metabolic gene expression programs among tumor subclones, immune infiltrates, and stromal cells.[126] Spatial transcriptomics and spatial metabolomics further localize these signatures within tissue architecture, revealing metabolic gradients driven by hypoxia, vascular proximity, and stromal

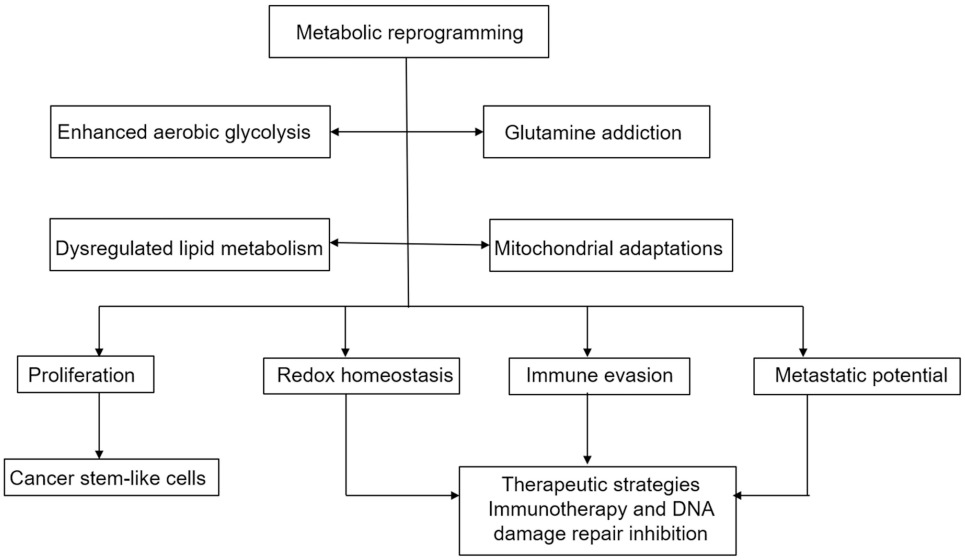

Figure 3 Integrative schematic illustrating key metabolic pathways altered in OC, their functional roles, and therapeutic implications. Metabolic reprogramming in OC includes enhanced aerobic glycolysis, glutamine addiction, dysregulated lipid metabolism, and mitochondrial adaptations. These alterations contribute to key cancer hallmarks, including proliferation, redox homeostasis, immune evasion, and metastatic potential. Notably, metabolic changes support the maintenance of cancer stem-like cells and facilitate resistance to therapy. The downstream effects of these processes create vulnerabilities that are currently being explored through therapeutic strategies, including immunotherapy and inhibitors targeting DNA damage repair pathways.

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Table 3 Technologies for Metabolic Profiling in OC

Technology	Key Features	Advantages	Applications in OC	References
LC-MS/MS Metabolomics	High-throughput detection of metabolites in tissues, plasma, ascites	Sensitive, quantitative, broad coverage	Identification of metabolic signatures predicting platinum resistance	[119]
Stable Isotope Tracing (eg, 13C-glucose)	Real-time tracking of metabolic fluxes	Reveals dynamic pathway utilization	Mapping carbon flow through glycolysis and TCA cycle in OC cells	[120,121]
Hyperpolarized 13C-MRI	Non-invasive imaging of real-time metabolic flux (eg, pyruvate-to-lactate conversion)	In vivo assessment, functional imaging	Monitoring therapeutic response based on glycolytic activity	[122]
PET Imaging (18F-FDG, 11C-acetate)	Visualizes glucose and lipid metabolism	Clinical availability, non-invasive staging	Diagnosis, monitoring metabolic changes during therapy	[123,124]
Single-cell RNA Sequencing (scRNA-seq)	Transcriptome profiling at single-cell resolution	Identifies intratumoral metabolic heterogeneity	Dissecting metabolic programs of tumor and immune cells	[123]
Spatial Transcriptomics / Spatial Metabolomics	Spatial mapping of gene expression or metabolite distribution	Preserves tissue architecture; detects metabolic gradients	Defining hypoxia/metabolism-associated tumor regions	[123,127]
Genome-scale Metabolic Modeling	Computational prediction of metabolic vulnerabilities based on multi-omics data	Integrates genomics, transcriptomics, metabolomics	Identifying targetable metabolic pathways and simulating drug response	[128,129]

interactions.[127] Computational approaches such as genome-scale metabolic models and flux balance analysis integrate multi-omics data to predict metabolic vulnerabilities and simulate drug response.[128,129] The key technologies currently employed for metabolic profiling in OC are summarized in Table 3.

Challenges and Future Perspectives

Despite significant progress, the clinical translation of metabolic targeting strategies in OC remains challenging. Intratumoral metabolic heterogeneity, characterized by spatial variation within tumors and dynamic adaptation over time, compromises the efficacy of monotherapies, as distinct subpopulations may rely on different fuel sources or rapidly reprogram their metabolism in response to therapeutic pressure, ultimately leading to resistance and disease recurrence. Single-cell and longitudinal profiling approaches will be critical to elucidate dominant and evolving metabolic dependencies, thereby informing more effective and durable therapeutic interventions.[126,128–131]

While several inhibitors demonstrate strong preclinical efficacy, many lack sufficient selectivity or tolerability in patients due to the shared reliance of normal tissues on core metabolic pathways.[132] Strategies that focus on cancer-specific metabolic adaptations or combine metabolic inhibitors with PARP inhibitors or immunotherapies may improve therapeutic windows and efficacy.[133]

The absence of validated metabolic biomarkers significantly impedes patient stratification and the optimization of treatment strategies in OC. Dynamic indicators, including serum metabolite ratios, imaging-derived metabolic activity such as FDG uptake, and gene expression signatures, offer promising avenues for enhancing clinical decision-making. However, the clinical utility of these biomarkers necessitates rigorous standardization and prospective validation to ensure their reliability and effectiveness in guiding therapeutic interventions.[119,124]

Designing effective clinical trials also remains complex. Trial frameworks must consider intratumoral heterogeneity, treatment-induced reprogramming, and compensatory metabolic shifts. Basket and umbrella trials that incorporate metabolic profiling may enhance patient selection and assess combination strategies involving DNA repair, angiogenesis, or immune checkpoint pathways.[134]

Ultimately, integrating spatial, temporal, and functional metabolic insights into clinical workflows will be crucial for identifying actionable vulnerabilities and advancing precision metabolic oncology.

Conclusion

Metabolic reprogramming is now recognized as a fundamental hallmark of OC, driving multiple aspects of tumor progression, from sustained proliferation and survival under stress to immune evasion, drug resistance, and metastatic dissemination.[14,15] OC cells exhibit remarkable metabolic plasticity, enabling them to toggle between glycolysis and OXPHOS, exploit amino acid and lipid sources, and dynamically adapt to microenvironmental and therapeutic pressures.[135] Key metabolic hallmarks such as enhanced glycolysis, elevated OXPHOS in chemoresistant clones,

glutamine addiction, and lipid utilization in metastatic cells, collectively establish a bioenergetic landscape that supports disease persistence and therapeutic failure.[136] CSCs rely on mitochondrial metabolism and redox control to maintain stemness and evade conventional therapies.[19] Concurrently, metabolic crosstalk with immune and stromal components further shapes an immunosuppressive and therapy-refractory tumor microenvironment.[15,137]

Therapeutically, these metabolic vulnerabilities represent a promising axis for intervention. Targeting glycolysis, glutaminolysis, fatty acid oxidation, or mitochondrial respiration, either individually or in combination, has shown potential to overcome platinum resistance, eradicate CSCs, and enhance the efficacy of immunotherapy.[138] In addition, synthetic lethality approaches that integrate metabolic inhibition with PARP inhibitors or redox modulators are actively being investigated.[139] For instance, inhibitors of glutaminase such as CB-839, fatty acid synthase inhibitors like TVB-2640, and monocarboxylate transporter inhibitors such as AZD3965 have demonstrated promising preclinical efficacy, particularly in combination with PARP inhibitors or immune checkpoint inhibitors.

As our understanding of tumor metabolism continues to evolve, future efforts must integrate spatial, temporal, and functional metabolic data with clinical insights to enable precision metabolic oncology. Key future directions include the development of robust metabolic biomarkers to guide patient stratification, real-time metabolic imaging for therapy monitoring, and validation of combinatorial strategies in clinical trials. A deeper understanding of inter-patient and intra-tumoral metabolic heterogeneity will also be critical for personalizing therapeutic interventions. Ultimately, leveraging the bioenergetic flexibility of OC as a therapeutic vulnerability may hold the key to improving long-term outcomes for patients with this aggressive disease.[44,140–142]

Author Contributions

All authors contributed significantly to this work, including its conception, study design, data acquisition, execution, analysis, and interpretation. Each author participated in drafting, revising, or critically reviewing the manuscript, approved the final version for publication, agreed on the journal of submission, and accepts full responsibility for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Mazidimoradi A, Momenimovahed Z, Allahqoli L, et al. The global, regional and national epidemiology, incidence, mortality, and burden of ovarian cancer. *Health Sci Rep*. 2022;5(6):e936. doi:10.1002/hsr2.936
2. Feng J, Xu L, Chen Y, Lin R, Li H, He H. Trends in incidence and mortality for ovarian cancer in China from 1990 to 2019 and its forecasted levels in 30 years. *J Ovarian Res*. 2023;16(1):139. doi:10.1186/s13048-023-01233-y
3. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
4. Labidi-Galy SI, Papp E, Hallberg D, et al. High grade serous ovarian carcinomas originate in the fallopian tube. *Nat Commun*. 2017;8(1):1093. doi:10.1038/s41467-017-00962-1
5. Bronder D, Tighe A, Wangsa D, et al. TP53 loss initiates chromosomal instability in fallopian tube epithelial cells. *Dis Model Mech*. 2021;14 (11). doi:10.1242/dmm.049001
6. Bergsten TM, Burdette JE, Dean M. Fallopian tube initiation of high grade serous ovarian cancer and ovarian metastasis: mechanisms and therapeutic implications. *Cancer Lett*. 2020;476:152–160. doi:10.1016/j.canlet.2020.02.017
7. Miras I, Estévez-García P, Muñoz-Galván S. Clinical and molecular features of platinum resistance in ovarian cancer. *Crit Rev Oncol/Hematol*. 2024;201:104434. doi:10.1016/j.critrevonc.2024.104434
8. Havasi A, Cainap SS, Havasi AT, Cainap C. Ovarian cancer-insights into platinum resistance and overcoming it. *Medicina*. 2023;59(3). doi:10.3390/medicina59030544
9. Matsuo K, Lin YG, Roman LD, Sood AK. Overcoming platinum resistance in ovarian carcinoma. *Expert Opin Investig Drugs*. 2010;19 (11):1339–1354. doi:10.1517/13543784.2010.515585
10. Aluloski I, Tanturovski M, Jovanovic R, et al. Survival of advanced stage high-grade serous ovarian cancer patients in the Republic of Macedonia. *Open Access Maced J Med Sci*. 2017;5(7):904–908. doi:10.3889/oamjms.2017.215
11. Wu Q, He X, Liu J, Ou C, Li Y, Fu X. Integrative evaluation and experimental validation of the immune-modulating potential of dysregulated extracellular matrix genes in high-grade serous ovarian cancer prognosis. *Can Cell Inter*. 2023;23(1):223. doi:10.1186/s12935-023-03061-y
12. Gutic B, Bozanovic T, Mandic A, et al. Preliminary outcomes of five-year survival for ovarian malignancies in profiled Serbian Oncology Centre. *Clinics*. 2023;78:100204. doi:10.1016/j.clinsp.2023.100204

13. Zhang H, Li S, Wang D, et al. Metabolic reprogramming and immune evasion: the interplay in the tumor microenvironment. *Biomarker Res*. 2024;12(1):96. doi:10.1186/s40364-024-00646-1
14. Zhang L, Zhao J, Su C, et al. Organoid models of ovarian cancer: resolving immune mechanisms of metabolic reprogramming and drug resistance. *Front Immunol*. 2025;16:1573686. doi:10.3389/fimmu.2025.1573686
15. Lin Y, Zhou X, Ni Y, Zhao X, Liang X. Metabolic reprogramming of the tumor immune microenvironment in ovarian cancer: a novel orientation for immunotherapy. *Front Immunol*. 2022;13:1030831. doi:10.3389/fimmu.2022.1030831
16. Frederick MI, Nassef MZ, Borrelli MJ, et al. Metabolic adaptation in epithelial ovarian cancer metastasis. *Biochim Biophys Acta Mol Basis Dis*. 2024;1870(7):167312. doi:10.1016/j.bbadis.2024.167312
17. Kim J, DeBerardinis RJ. Mechanisms and implications of metabolic heterogeneity in cancer. *Cell Metab*. 2019;30(3):434–446. doi:10.1016/j.cmet.2019.08.013
18. Mei S, Chen X, Wang K, Chen Y. Tumor microenvironment in ovarian cancer peritoneal metastasis. *Can Cell Inter*. 2023;23(1):11. doi:10.1186/s12935-023-02854-5
19. Pastò A, Bellio C, Pilotto G, et al. Cancer stem cells from epithelial ovarian cancer patients privilege oxidative phosphorylation, and resist glucose deprivation. *Oncotarget*. 2014;5(12):4305–4319. doi:10.18632/oncotarget.2010
20. Murali R, Balasubramaniam V, Srinivas S, et al. Deregulated metabolic pathways in ovarian cancer: cause and consequence. *Metabolites*. 2023;13(4). doi:10.3390/metabo13040560
21. Xiang J, Zhou L, He Y, Wu S. LDH-A inhibitors as remedies to enhance the anticancer effects of PARP inhibitors in ovarian cancer cells. *Aging*. 2021;13(24):25920–25930. doi:10.18632/aging.203780
22. Falchook G, Infante J, Arkenau H-T, et al. First-in-human study of the safety, pharmacokinetics, and pharmacodynamics of first-in-class fatty acid synthase inhibitor TVB-2640 alone and with a taxane in advanced tumors. *eClinicalMedicine*. 2021;34. doi:10.1016/j.eclinm.2021.100797
23. Yuan L, Sheng X, Clark LH, et al. Glutaminase inhibitor compound 968 inhibits cell proliferation and sensitizes paclitaxel in ovarian cancer. *Am J Transl Res*. 2016;8(10):4265–4277.
24. Danzi F, Pacchiana R, Mafficini A, et al. To metabolomics and beyond: a technological portfolio to investigate cancer metabolism. *Signal Transduct Target Ther*. 2023;8(1):137. doi:10.1038/s41392-023-01380-0
25. Tufail M, Jiang C-H, Li N. Altered metabolism in cancer: insights into energy pathways and therapeutic targets. *Mol Cancer*. 2024;23(1):203. doi:10.1186/s12943-024-02119-3
26. Nantasupha C, Thonusin C, Charoenkwan K, Chattipakorn S, Chattipakorn N. Metabolic reprogramming in epithelial ovarian cancer. *Am J Transl Res*. 2021;13(9):9950–9973.
27. Siu MKY, Jiang Y-X, Wang -J-J, et al. Hexokinase 2 regulates ovarian cancer cell migration, invasion and stemness via FAK/ERK1/2/MMP9/NANOG/SOX9 signaling cascades. *Cancers*. 2019;11(6). doi:10.3390/cancers11060813
28. Li F-L, Liu J-P, Bao R-X, et al. Acetylation accumulates PFKFB3 in cytoplasm to promote glycolysis and protects cells from cisplatin-induced apoptosis. *Nat Commun*. 2018;9(1):508. doi:10.1038/s41467-018-02950-5
29. Shim H, Oishi S, Fujii N. Chemokine receptor CXCR4 as a therapeutic target for neuroectodermal tumors. *Semi Cancer Biol*. 2009;19(2):123–134. doi:10.1016/j.semcancer.2008.11.004
30. Le A, Cooper CR, Gouw AM, et al. Inhibition of lactate dehydrogenase A induces oxidative stress and inhibits tumor progression. *Proc Natl Acad Sci U S A*. 2010;107(5):2037–2042. doi:10.1073/pnas.0914433107
31. Masoud GN, Li W. HIF-1α pathway: role, regulation and intervention for cancer therapy. *Acta Pharm Sin B*. 2015;5(5):378–389. doi:10.1016/j.apsb.2015.05.007
32. Stine ZE, Walton ZE, Altman BJ, Hsieh AL, Dang CV. MYC, metabolism, and cancer. *Cancer Discov*. 2015;5(10):1024–1039. doi:10.1158/2159-8290.Cd-15-0507
33. Rankin EB, Giaccia AJ. Hypoxic control of metastasis. *Science*. 2016;352(6282):175–180. doi:10.1126/science.aaf4405
34. Li F, Wang Y, Zeller KI, et al. Myc stimulates nuclearly encoded mitochondrial genes and mitochondrial biogenesis. *Mol Cell Biol*. 2005;25(14):6225–6234. doi:10.1128/mcb.25.14.6225-6234.2005
35. Wise DR, DeBerardinis RJ, Mancuso A, et al. Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. *Proc Natl Acad Sci U S A*. 2008;105(48):18782–18787. doi:10.1073/pnas.0810199105
36. Jiang YX, Siu MKY, Wang JJ, et al. PFKFB3 regulates chemoresistance, metastasis and stemness via IAP proteins and the NF-κB signaling pathway in ovarian cancer. *Front Oncol*. 2022;12:748403. doi:10.3389/fonc.2022.748403
37. Dar S, Chhina J, Mert I, et al. Bioenergetic adaptations in chemoresistant ovarian cancer cells. *Sci Rep*. 2017;7(1):8760. doi:10.1038/s41598-017-09206-0
38. Emmings E, Mullany S, Chang Z, Landen CN, Linder S, Bazzaro M. Targeting mitochondria for treatment of chemoresistant ovarian cancer. *Int J Mol Sci*. 2019;20(1). doi:10.3390/ijms20010229
39. Sriramkumar S, Sood R, Huntington TD, et al. Platinum-induced mitochondrial OXPHOS contributes to cancer stem cell enrichment in ovarian cancer. *J Transl Med*. 2022;20(1):246. doi:10.1186/s12967-022-03447-y
40. Zou GP, Yu CX, Shi SL, et al. Mitochondrial dynamics mediated by DRP1 and MFN2 contributes to cisplatin chemoresistance in human ovarian cancer SKOV3 cells. *J Cancer*. 2021;12(24):7358–7373. doi:10.7150/jca.61379
41. Baumann K, Pfisterer J, Wimberger P, et al. Intraperitoneal treatment with the trifunctional bispecific antibody catumaxomab in patients with platinum-resistant epithelial ovarian cancer: a phase IIa study of the AGO Study Group. *Gynecologic Oncol*. 2011;123(1):27–32. doi:10.1016/j.ygyno.2011.06.004
42. Pujalte-Martin M, Belaïd A, Bost S, et al. Targeting cancer and immune cell metabolism with the complex I inhibitors metformin and IACS-010759. *Mol Oncol*. 2024;18(7):1719–1738. doi:10.1002/1878-0261.13583
43. Bellio C, DiGloria C, Spriggs DR, Foster R, Growdon WB, Rueda BR. The metabolic inhibitor CPI-613 negates treatment enrichment of ovarian cancer stem cells. *Cancers*. 2019;11(11). doi:10.3390/cancers11111678
44. Udumula MP, Rashid F, Singh H, et al. Targeting mitochondrial metabolism with CPI-613 in chemoresistant ovarian tumors. *J Ovarian Res*. 2024;17(1):226. doi:10.1186/s13048-024-01546-6
45. Sun L, Yin Y, Clark LH, et al. Dual inhibition of glycolysis and glutaminolysis as a therapeutic strategy in the treatment of ovarian cancer. *Oncotarget*. 2017;8(38):63551–63561. doi:10.18632/oncotarget.18854

46. Fasoulakis Z, Koutras A, Ntounis T, et al. Ovarian cancer and glutamine metabolism. *Int J Mol Sci*. 2023;24(5). doi:10.3390/ijms24055041
47. Saha SK, Islam SMR, Abdullah-Al-Wadud M, Islam S, Ali F, Park KS. Multiomics analysis reveals that GLS and GLS2 differentially modulate the clinical outcomes of cancer. *J Clin Med*. 2019;8(3). doi:10.3390/jcm8030355
48. Clemente V, Hoshino A, Shetty M, et al. GLS1 is a protective factor in patients with ovarian clear cell carcinoma and its expression does not correlate with ARID1A-mutated tumors. *Cancer Res Commun*. 2022;2(8):784–794. doi:10.1158/2767-9764.crc-22-0122
49. Raninga PV, He Y, Datta KK, et al. Combined thioredoxin reductase and glutaminase inhibition exerts synergistic anti-tumor activity in MYC-high high-grade serous ovarian carcinoma. *Mol Ther*. 2023;31(3):729–743. doi:10.1016/j.ymthe.2022.12.011
50. Amelio I, Cutruzzolá F, Antonov A, Agostini M, Melino G. Serine and glycine metabolism in cancer. *Trends Biochem Sci*. 2014;39(4):191–198. doi:10.1016/j.tibs.2014.02.004
51. Pan S, Fan M, Liu Z, Li X, Wang H. Serine, glycine and one-carbon metabolism in cancer (Review). *Int J Oncol*. 2021;58(2):158–170. doi:10.3892/ijo.2020.5158
52. Bi F, An Y, Sun T, You Y, Yang Q. PHGDH is upregulated at translational level and implicated in platin-resistant in ovarian cancer cells. *Front Oncol*. 2021;11:643129. doi:10.3389/fonc.2021.643129
53. Zhang X, Wang Z. Targeting SHMTs and MTHFDs in cancer: attractive opportunity for anti-tumor strategy. *Front Pharmacol*. 2024;15:1335785. doi:10.3389/fphar.2024.1335785
54. Amobi-McCloud A, Muthuswamy R, Battaglia S, et al. IDO1 expression in ovarian cancer induces PD-1 in T cells via aryl hydrocarbon receptor activation. *Front Immunol*. 2021;12:678999. doi:10.3389/fimmu.2021.678999
55. Zhang S, Gao Y, Wang P, et al. Tryptophan metabolism enzymes are potential targets in ovarian clear cell carcinoma. *Cancer Med*. 2023;12 (24):21996–22005. doi:10.1002/cam4.6778
56. Yoon H, Lee S. Fatty acid metabolism in ovarian cancer: therapeutic implications. *Int J Mol Sci*. 2022;23(4). doi:10.3390/ijms23042170
57. Ladanyi A, Mukherjee A, Kenny HA, et al. Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis. *Oncogene*. 2018;37(17):2285–2301. doi:10.1038/s41388-017-0093-z
58. Jiang L, Wang H, Li J, et al. Up-regulated FASN expression promotes transcoelomic metastasis of ovarian cancer cell through epithelial-mesenchymal transition. *Int J Mol Sci*. 2014;15(7):11539–11554. doi:10.3390/ijms150711539
59. Cai Y, Wang J, Zhang L, et al. Expressions of fatty acid synthase and HER2 are correlated with poor prognosis of ovarian cancer. *Med Oncol*. 2015;32(1):391. doi:10.1007/s12032-014-0391-z
60. Zhu Y, Chen S, Su H, et al. CPT1A-mediated MFF succinylation promotes stemness maintenance in ovarian cancer stem cells. *Commun Biol*. 2025;8(1):250. doi:10.1038/s42003-025-07720-w
61. Sawyer BT, Qamar L, Yamamoto TM, et al. Targeting fatty acid oxidation to promote anoikis and inhibit ovarian cancer progression. *Mol Cancer Res*. 2020;18(7):1088–1098. doi:10.1158/1541-7786.Mcr-19-1057
62. Cui X, Cao C, Li X, Lin B, Yan A, Yang Y. Succinylation of 14-3-3 theta by CPT1A promotes survival and paclitaxel resistance in nasal type extranodal natural killer/T-cell lymphoma. *Transl Oncol*. 2024;46:102006. doi:10.1016/j.tranon.2024.102006
63. Ramakrishnan R, Tyurin VA, Veglia F, et al. Oxidized lipids block antigen cross-presentation by dendritic cells in cancer. *J Immunol*. 2014;192 (6):2920–2931. doi:10.4049/jimmunol.1302801
64. Herber DL, Cao W, Nefedova Y, et al. Lipid accumulation and dendritic cell dysfunction in cancer. *Nat Med*. 2010;16(8):880–886. doi:10.1038/nm.2172
65. Ma Q, Liu Z, Wang T, et al. Resensitizing paclitaxel-resistant ovarian cancer via targeting lipid metabolism key enzymes CPT1A, SCD and FASN. *Int J Mol Sci*. 2023;24(22). doi:10.3390/ijms242216503
66. Garlisi B, Lauks S, Aitken C, et al. The complex tumor microenvironment in ovarian cancer: therapeutic challenges and opportunities. *Curr Oncol*. 2024;31(7):3826–3844. doi:10.3390/curroncol31070283
67. Lin Y, Liang X, Zhang X, Ni Y, Zhou X, Zhao X. Metabolic cross-talk between ovarian cancer and the tumor microenvironment-providing potential targets for cancer therapy. *Front Biosci*. 2022;27(4):139. doi:10.31083/j.fbl2704139
68. Wang ZH, Peng WB, Zhang P, Yang XP, Zhou Q. Lactate in the tumour microenvironment: from immune modulation to therapy. *EBioMedicine*. 2021;73:103627. doi:10.1016/j.ebiom.2021.103627
69. Peralta RM, Xie B, Lontos K, et al. Dysfunction of exhausted T cells is enforced by MCT11-mediated lactate metabolism. *Nat Immunol*. 2024;25(12):2297–2307. doi:10.1038/s41590-024-01999-3
70. Hu X, Huang Z, Li L. LDHB mediates histone lactylation to activate PD-L1 and promote ovarian cancer immune escape. *Cancer Invest*. 2025;43(1):70–79. doi:10.1080/07357907.2024.2430283
71. Abiko K, Mandai M, Hamanishi J, et al. PD-L1 on tumor cells is induced in ascites and promotes peritoneal dissemination of ovarian cancer through CTL dysfunction. *Clin Cancer Res*. 2013;19(6):1363–1374. doi:10.1158/1078-0432.Ccr-12-2199
72. He Z, Zhang S. Tumor-associated macrophages and their functional transformation in the hypoxic tumor microenvironment. *Front Immunol*. 2021;12:741305. doi:10.3389/fimmu.2021.741305
73. Colegio OR, Chu NQ, Szabo AL, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature*. 2014;513(7519):559–563. doi:10.1038/nature13490
74. Yan Y, Huang L, Liu Y, et al. Metabolic profiles of regulatory T cells and their adaptations to the tumor microenvironment: implications for antitumor immunity. *J Hematol Oncol*. 2022;15(1):104. doi:10.1186/s13045-022-01322-3
75. Okła K. Myeloid-Derived Suppressor Cells (MDSCs) in ovarian cancer-looking back and forward. *Cells*. 2023;12(14). doi:10.3390/cells12141912
76. Chatterjee P, Bhowmik D, Roy SS. A systemic analysis of monocarboxylate transporters in ovarian cancer and possible therapeutic interventions. *Channels*. 2023;17(1):2273008. doi:10.1080/19336950.2023.2273008
77. Wang H, Luo Y, Ran R, et al. IDO1 modulates the sensitivity of epithelial ovarian cancer cells to cisplatin through ROS/p53-dependent apoptosis. *Int J Mol Sci*. 2022;23(19). doi:10.3390/ijms231912002
78. Nieman KM, Kenny HA, Penicka CV, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nature Med*. 2011;17(11):1498–1503. doi:10.1038/nm.2492
79. Mukherjee A, Chiang CY, Daifotis HA, et al. Adipocyte-induced FABP4 expression in ovarian cancer cells promotes metastasis and mediates carboplatin resistance. *Cancer Res*. 2020;80(8):1748–1761. doi:10.1158/0008-5472.Can-19-1999
80. Liang L, Li W, Li X, et al. 'Reverse Warburg effect' of cancer-associated fibroblasts. *Int J Oncol*. 2022;60(6). doi:10.3892/ijo.2022.5357

81. Niu N, Yao J, Bast R, Sood A, Liu J. IL-6 promotes drug resistance through formation of polyploid giant cancer cells and stromal fibroblast reprogramming. *Oncogenesis*. 2021;10:65. doi:10.1038/s41389-021-00349-4
82. Nishiwaki N, Noma K, Ohara T, et al. Overcoming cancer-associated fibroblast-induced immunosuppression by anti-interleukin-6 receptor antibody. *Cancer Immunol Immunother*. 2023;72(7):2029–2044. doi:10.1007/s00262-023-03378-7
83. Croizer H, Mhaidly R, Kieffer Y, et al. Deciphering the spatial landscape and plasticity of immunosuppressive fibroblasts in breast cancer. *Nat Commun*. 2024;15(1):2806. doi:10.1038/s41467-024-47068-z
84. Akinjiyan FA, Ibitoye Z, Zhao P, et al. DDR2-regulated arginase activity in ovarian cancer-associated fibroblasts promotes collagen production and tumor progression. *Oncogene*. 2024;43(3):189–201. doi:10.1038/s41388-023-02884-3
85. Wang X, Du ZW, Xu TM, et al. HIF-1α is a rational target for future ovarian cancer therapies. *Front Oncol*. 2021;11:785111. doi:10.3389/fonc.2021.785111
86. Wang Y, Yun Y, Wu B, et al. FOXM1 promotes reprogramming of glucose metabolism in epithelial ovarian cancer cells via activation of GLUT1 and HK2 transcription. *Oncotarget*. 2016;7(30):47985–47997. doi:10.18632/oncotarget.10103
87. Gao T, Zhang X, Zhao J, et al. SIK2 promotes reprogramming of glucose metabolism through PI3K/AKT/HIF-1α pathway and Drp1-mediated mitochondrial fission in ovarian cancer. *Cancer Lett*. 2020;469:89–101. doi:10.1016/j.canlet.2019.10.029
88. Koc ZC, Sollars VE, Bou Zgheib N, Rankin GO, Koc EC. Evaluation of mitochondrial biogenesis and ROS generation in high-grade serous ovarian cancer. *Front Oncol*. 2023;13:1129352. doi:10.3389/fonc.2023.1129352
89. Ahmed N, Kadife E, Raza A, Short M, Jubinsky PT, Kannourakis G. Ovarian cancer, cancer stem cells and current treatment strategies: a potential role of magmas in the current treatment methods. *Cells*. 2020;9(3). doi:10.3390/cells9030719
90. Tan DS, Agarwal R, Kaye SB. Mechanisms of transcoelomic metastasis in ovarian cancer. *Lancet Oncol*. 2006;7(11):925–934. doi:10.1016/s1470-2045(06)70939-1
91. Ghoneum A, Gonzalez D, Abdulfattah AY, Said N. Metabolic plasticity in ovarian cancer stem cells. *Cancers*. 2020;12(5). doi:10.3390/cancers12051267
92. Zaidi NE, Shazali NAH, Leow TC, et al. CD36-fatty acid-mediated metastasis via the bidirectional interactions of cancer cells and macrophages. *Cells*. 2022;11(22). doi:10.3390/cells11223556
93. Feng WW, Zuppe HT, Kurokawa M. The role of CD36 in cancer progression and its value as a therapeutic target. *Cells*. 2023;12(12). doi:10.3390/cells12121605
94. Suzuki T, Conant A, Curow C, Alexander A, Ioffe Y, Unternaehrer JJ. Role of epithelial-mesenchymal transition factor SNAI1 and its targets in ovarian cancer aggressiveness. *J Cancer Metastasis Treat*. 2023;9. doi:10.20517/2394-4722.2023.34
95. Sun NY, Yang MH. Metabolic reprogramming and epithelial-mesenchymal plasticity: opportunities and challenges for cancer therapy. *Front Oncol*. 2020;10:792. doi:10.3389/fonc.2020.00792
96. Bhattacharya D, Scimè A. Metabolic regulation of epithelial to mesenchymal transition: implications for endocrine cancer. *Front Endocrinol*. 2019;10:773. doi:10.3389/fendo.2019.00773
97. Loret N, Denys H, Tummers P, Berx G. The role of epithelial-to-mesenchymal plasticity in ovarian cancer progression and therapy resistance. *Cancers*. 2019;11(6):838. doi:10.3390/cancers11060838
98. Liao J, Qian F, Tchabo N, et al. Ovarian cancer spheroid cells with stem cell-like properties contribute to tumor generation, metastasis and chemotherapy resistance through hypoxia-resistant metabolism. *PLoS One*. 2014;9(1):e84941. doi:10.1371/journal.pone.0084941
99. Chaudhry S, Thomas SN, Simmons Jr GE. Targeting lipid metabolism in the treatment of ovarian cancer. *Oncotarget*. 2022;13(1):768–783. doi:10.18632/oncotarget.28241
100. Zhu J, Zheng Y, Zhang H, Sun H. Targeting cancer cell metabolism: the combination of metformin and 2-Deoxyglucose regulates apoptosis in ovarian cancer cells via p38 MAPK/JNK signaling pathway. *Am J Transl Res*. 2016;8(11):4812–4821.
101. Xiao Y, Wu Y, Wang Q, Li M, Deng C, Gu X. Repression of PFKFB3 sensitizes ovarian cancer to PARP inhibitors by impairing homologous recombination repair. *Cell Commun Signal*. 2025;23(1):48. doi:10.1186/s12964-025-02056-8
102. Yap TA, Daver N, Mahendra M, et al. Complex I inhibitor of oxidative phosphorylation in advanced solid tumors and acute myeloid leukemia: Phase I trials. *Nature Med*. 2023;29(1):115–126. doi:10.1038/s41591-022-02103-8
103. Kleih M, Böpple K, Dong M, et al. Direct impact of cisplatin on mitochondria induces ROS production that dictates cell fate of ovarian cancer cells. *Cell Death Dis*. 2019;10(11):851. doi:10.1038/s41419-019-2081-4
104. Wu H, Zhang J, Wang Q, Li Z, Li L, Xie Y. Metformin combined with CB-839 specifically inhibits KRAS-mutant ovarian cancer. *Sci Rep*. 2025;15(1):6072. doi:10.1038/s41598-025-90963-8
105. Xu X, Meng Y, Li L, et al. Overview of the development of glutaminase inhibitors: achievements and future directions. *J Med Chem*. 2019;62(3):1096–1115. doi:10.1021/acs.jmedchem.8b00961
106. Zaytseva YY, Rychahou PG, Le AT, et al. Preclinical evaluation of novel fatty acid synthase inhibitors in primary colorectal cancer cells and a patient-derived xenograft model of colorectal cancer. *Oncotarget*. 2018;9(37):24787–24800. doi:10.18632/oncotarget.25361
107. Falchook G, Infante J, Arkenau HT, et al. First-in-human study of the safety, pharmacokinetics, and pharmacodynamics of first-in-class fatty acid synthase inhibitor TVB-2640 alone and with a taxane in advanced tumors. *EClinicalMedicine*. 2021;34:100797. doi:10.1016/j.eclinm.2021.100797
108. Lin H, Wang L, Chen H, et al. Mitochondrial fatty acid oxidation as the target for blocking therapy-resistance and inhibiting tumor recurrence: the proof-of-principle model demonstrated for ovarian cancer cells. *J Adv Res*. 2025. doi:10.1016/j.jare.2025.03.026
109. Hou D, Liu Z, Xu X, et al. Increased oxidative stress mediates the antitumor effect of PARP inhibition in ovarian cancer. *Redox Biol*. 2018;17:99–111. doi:10.1016/j.redox.2018.03.016
110. Wang C, Gao P, Xu J, et al. Natural phytochemicals prevent side effects in BRCA-mutated ovarian cancer and PARP inhibitor treatment. *Front Pharmacol*. 2022;13:1078303. doi:10.3389/fphar.2022.1078303
111. Xiao F, Wang Z, Qiao L, et al. Application of PARP inhibitors combined with immune checkpoint inhibitors in ovarian cancer. *J Transl Med*. 2024;22(1):778. doi:10.1186/s12967-024-05583-z
112. Bose S, Huang Q, Ma Y, et al. G6PD inhibition sensitizes ovarian cancer cells to oxidative stress in the metastatic omental microenvironment. *Cell Rep*. 2022;39(13):111012. doi:10.1016/j.celrep.2022.111012

113. Catanzaro D, Gaude E, Orso G, et al. Inhibition of glucose-6-phosphate dehydrogenase sensitizes cisplatin-resistant cells to death. *Oncotarget*. 2015;6(30):30102–30114. doi:10.18632/oncotarget.4945
114. Nacarelli T, Fukumoto T, Zundell JA, et al. NAMPT inhibition suppresses cancer stem-like cells associated with therapy-induced senescence in ovarian cancer. *Cancer Res*. 2020;80(4):890–900. doi:10.1158/0008-5472.Can-19-2830
115. Liu Q, Liu Z, Zhang X, Zeng A, Song L. Revisiting of cancer immunotherapy: insight from the dialogue between glycolysis and PD-1/PD-L1 axis in the tumor microenvironment. *Int J Biol Sci*. 2025;21(3):1202–1221. doi:10.7150/ijbs.104079
116. Kristeleit R, Davidenko I, Shirinkin V, et al. A randomised, open-label, Phase 2 study of the IDO1 inhibitor epacadostat (INCB024360) versus tamoxifen as therapy for biochemically recurrent (CA-125 relapse)-only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer. *Gynecol Oncol*. 2017;146(3):484–490. doi:10.1016/j.ygyno.2017.07.005
117. Odunsi K, Qian F, Lugade AA, et al. Metabolic adaptation of ovarian tumors in patients treated with an IDO1 inhibitor constrains antitumor immune responses. *Sci Transl Med*. 2022;14(636):eabg8402. doi:10.1126/scitranslmed.abg8402
118. Zeng Y, Li B, Liang Y, et al. Dual blockade of CXCL12-CXCR4 and PD-1-PD-L1 pathways prolongs survival of ovarian tumor-bearing mice by prevention of immunosuppression in the tumor microenvironment. *FASEB j*. 2019;33(5):6596–6608. doi:10.1096/fj.201802067RR
119. Ahmed-Salim Y, Galazis N, Bracewell-Milnes T, et al. The application of metabolomics in ovarian cancer management: a systematic review. *Int J Gynecol Cancer*. 2021;31(5):754–774. doi:10.1136/ijgc-2020-001862
120. Hilovsky D, Hartsell J, Young JD, Liu X. Stable isotope tracing analysis in cancer research: advancements and challenges in identifying dysregulated cancer metabolism and treatment strategies. *Metabolites*. 2024;14(6). doi:10.3390/metabo14060318
121. Antoniewicz MR. A guide to 13C metabolic flux analysis for the cancer biologist. *Exp Mol Med*. 2018;50(4):1–13. doi:10.1038/s12276-018-0060-y
122. Lai Y-C, Hsieh C-Y, Juan Y-H, et al. Hyperpolarized carbon-13 magnetic resonance imaging: technical considerations and clinical applications. *Korean J Radiol*. 2024;25(5):459–472.
123. Deford-Watts LM, Mintz A, Kridel SJ. The potential of ^{11}C-acetate PET for monitoring the fatty acid synthesis pathway in tumors. *Curr Pharm Biotechnol*. 2013;14(3):300–312. doi:10.2174/1389201011314030006
124. Ye S, Liu S, Xiang L, Wu X, Yang H. 18F-FDG PET/CT-based metabolic metrics in recurrent tumors of ovarian clear cell carcinoma and their prognostic implications. *BMC Cancer*. 2019;19(1):226. doi:10.1186/s12885-019-5441-7
125. Chia ML, Bulat F, Gaunt A, et al. Metabolic imaging distinguishes ovarian cancer subtypes and detects their early and variable responses to treatment. *Oncogene*. 2025;44(9):563–574. doi:10.1038/s41388-024-03231-w
126. Denisenko E, De kock L, Tan A, et al. Spatial transcriptomics reveals discrete tumour microenvironments and autocrine loops within ovarian cancer subclones. *Nat Commun*. 2024;15(1):2860. doi:10.1038/s41467-024-47271-y
127. Cilento MA, Sweeney CJ, Butler LM. Spatial transcriptomics in cancer research and potential clinical impact: a narrative review. *J Cancer Res Clin Oncol*. 2024;150(6):296. doi:10.1007/s00432-024-05816-0
128. Arora G, Banerjee M, Langthasa J, Bhat R, Chatterjee S. Targeting metabolic fluxes reverts metastatic transitions in ovarian cancer. *iScience*. 2023;26(11):108081. doi:10.1016/j.isci.2023.108081
129. Meeson KE, Schwartz J-M. Constraint-based modelling predicts metabolic signatures of low and high-grade serous ovarian cancer. *Npj Syst Biol Appl*. 2024;10(1):96. doi:10.1038/s41540-024-00418-5
130. Demicco M, Liu X-Z, Leithner K, Fendt S-M. Metabolic heterogeneity in cancer. *Nat Metab*. 2024;6(1):18–38. doi:10.1038/s42255-023-00963-z
131. Shao W, Lin Z, Xiahou Z, et al. Single-cell RNA sequencing reveals that MYBL2 in malignant epithelial cells is involved in the development and progression of ovarian cancer. *Front Immunol*. 2024;15:1438198. doi:10.3389/fimmu.2024.1438198
132. DePeaux K, Delgoffe GM. Metabolic barriers to cancer immunotherapy. *Nat Rev Immunol*. 2021;21(12):785–797. doi:10.1038/s41577-021-00541-y
133. Xie Y, Xiao D, Li D, et al. Combined strategies with PARP inhibitors for the treatment of BRCA wide type cancer. *Front Oncol*. 2024;14:1441222. doi:10.3389/fonc.2024.1441222
134. Duan X-P, Qin B-D, Jiao X-D, Liu K, Wang Z, Zang Y-S. New clinical trial design in precision medicine: discovery, development and direction. *Signal Transduct Target Ther*. 2024;9(1):57. doi:10.1038/s41392-024-01760-0
135. Avagliano A, Fiume G, Pelagalli A, et al. Metabolic plasticity of melanoma cells and their crosstalk with tumor microenvironment. *Front Oncol*. 2020;10:722. doi:10.3389/fonc.2020.00722
136. Tan Y, Li J, Zhao G, et al. Metabolic reprogramming from glycolysis to fatty acid uptake and beta-oxidation in platinum-resistant cancer cells. *Nat Commun*. 2022;13(1):4554. doi:10.1038/s41467-022-32101-w
137. Tang PW, Frisbie L, Hempel N, Coffman L. Insights into the tumor-stromal-immune cell metabolism cross talk in ovarian cancer. *Am J Physiol Cell Physiol*. 2023;325(3):C731–c749. doi:10.1152/ajpcell.00588.2022
138. Hudson CD, Savadelis A, Nagaraj AB, et al. Altered glutamine metabolism in platinum resistant ovarian cancer. *Oncotarget*. 2016;7(27):41637–41649. doi:10.18632/oncotarget.9317
139. Chandrasekaran A, Elias KM. Synthetic Lethality in Ovarian Cancer. *Mol Cancer Ther*. 2021;20(11):2117–2128. doi:10.1158/1535-7163.Mct-21-0500
140. Corvigno S, Badal S, Spradlin ML, et al. In situ profiling reveals metabolic alterations in the tumor microenvironment of ovarian cancer after chemotherapy. *Npj Precision Oncol*. 2023;7(1):115. doi:10.1038/s41698-023-00454-0
141. Kobayashi H, Yoshimoto C, Matsubara S, Shigetomi H, Imanaka S. A comprehensive overview of recent developments on the mechanisms and pathways of ferroptosis in cancer: the potential implications for therapeutic strategies in ovarian cancer. *Cancer Drug Resist*. 2023;6(3):547–566. doi:10.20517/cdr.2023.49
142. Gong D, Arbesfeld-Qiu JM, Perrault E, Bae JW, Hwang WL. Spatial oncology: translating contextual biology to the clinic. *Cancer Cell*. 2024;42(10):1653–1675. doi:10.1016/j.ccell.2024.09.001