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Review Article

Cancer-associated adipocytes in the ovarian cancer microenvironment

Qiuling Cai[1], Jing Yang[1], Huiling Shen[2], Wenlin Xu[1]

[1]*Department of Central Laboratory, The Fourth Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, China;*
[2]*Department of Oncology, The First Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu, China*

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Abstract: The tumor microenvironment (TME) plays a critical role in high energy metabolism during tumorigenesis, progression and metastasis. Among them, adipocytes, as an important component of the TME, can transform into cancer-associated adipocytes (CAAs) through dedifferentiation via interactions with tumor cells. These CAAs provide nutrients, growth factors, cytokines and metabolites to the tumor and later transdifferentiate into other stromal cells at a later stage to alter tumor growth, metastasis and the drug response and ultimately influence the treatment and prognosis of ovarian cancer. This review outlines the physiological functions of CAAs and discusses the progress in the use of CAAs as therapeutic targets in ovarian cancer.

Keywords: Adipocytes, adipokines, ovarian cancer, treatment of ovarian cancer, cancer-associated adipocytes

Introduction

Ovarian cancer (OC) is among the three most common fatal malignant gynecological cancers and poses a significant risk to women's health [1]. Ovarian malignancies comprise a variety of pathological forms, with epithelial ovarian cancer (EOC) being the most common, accounting for approximately 80% of ovarian malignancies [2]. The occurrence of OC is asymptomatic, and the majority of patients are clinically diagnosed at an advanced stage when metastasis and spread have already occurred, resulting in 4.4% of cancer-related deaths [3]. The elevated mortality rate is likely due to various factors, including chemoresistance and significant intraperitoneal metastasis [1]. Debulking surgery and platinum-taxane maintenance chemotherapy are the current front-line standards of therapy. Maintenance therapy with antivascular drugs or PARP inhibitors has also been shown to prolong progression-free survival (PFS) [4].

As with many other tumor types, OC grows in close proximity to an anatomy rich in adipose tissue, and its unique site of metastasis is the omentum [5]. An outstanding characteristic of the greater omentum is its adipose tissue, which can provide energy for tumor cells and create a more invasive microenvironment for tumor progression [6]. Clinical observations and retrospective clinical studies have shown that EOC rarely metastasizes outside the peritoneal adipocyte-rich environment; thus, OC does not follow classical lymphatic and blood metastatic routes but rather has a specific intraperitoneal dissemination route. Metastases can spread through the peritoneal cavity and into omental adipose tissue, which is rich in adipose-derived stem/stromal cells (ADSCs) [7]. Subsequently, the continuous paracrine secretion of extracellular vesicles (EVs) yields a variety of secretory factors and metabolites that enhance the proliferation of OC cells and promote their transformation to a highly invasive and metastatic phenotype [8].

The tumor microenvironment (TME) is a complex network of adipocytes, fibroblasts, vascular endothelial cells, immune cells and extracellular matrix proteins that creates conditions favoring the emergence of malignant clones [9]. An increasing number of studies have confirmed that cancer-associated adipocytes (CAAs), an essential component of the TME, play a role in the progression of OC [10]. Upon the invasion of tumor-adjacent adipocytes by tumor cells, the downregulation of terminal

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differentiation marker genes, such as peroxisome proliferator-activated receptor-γ (PPAR-γ) and CCAAT/enhancer binding protein-α (C/EBP-α), leads to dedifferentiation into preadipocytes or reprogramming into CAAs [11]. Abnormal energy metabolism in malignant tumors and the TME can lead to abnormally active lipolysis of CAAs. CAAs secrete tumor-associated adipokines, inflammatory factors, and exosomes and act as fuel reservoirs to promote tumor cell proliferation, invasion, angiogenesis, immune escape and drug resistance. Mature adipocytes consequently develop further, lose their lipid content, and show fibroblast-like associated properties [12]. This review provides an overview of the progress in research on the role of adipocytes in OC, specifically how CAAs significantly affect the biological behavior and prognosis of OC, and analyses the potential of adipocytes as a therapeutic target for treating OC.

Mature adipocytes vs. CAAs

As a near neighbor to ovarian epithelial cells, the adipose microenvironment serves as the preferred site for OC metastasis and the most frequent location for residual and recurrent disease. Adipocytes in the TME modified by tumor cells are referred to academically as CAAs, which are formed based on the dedifferentiation of adipocytes, mainly through the following related mechanisms: the WNT-PCP signaling pathway, the WNT/β-catenin signaling pathway, and tumor-derived exosomes [13]. In terms of cellular morphology, mature adipocytes comprise predominantly white adipose tissue, that is similar in size to normal cells, with round and large monolipid droplets [14]. Compared with mature adipocytes, CAAs exhibit an irregular shape, smaller volume, and small, dispersed lipid droplets [15]. Functionally, mature adipocytes possess endocrine functions. The expression and secretion of associated adipokines can regulate physiological functions such as appetite, immunity, coagulation, vascular tone and metabolic balance [16]. However, after tumor cells invade neighboring adipocytes, the expression of adipocyte differentiation markers, such as adiponectin, resistin and fatty acid binding protein (FABP4 or adipocyte protein 2, aP2), is initially reduced. Subsequently, the levels of their transcriptional regulators, PPAR-γ and C/EBP-α, are also decreased, and these cells in turn dedifferentiate into preadipocytes or are reprogrammed into CAAs [17]. CAAs exhibit a series of characteristics, including overexpression of inflammatory cytokines and proteases, as well as the differential expression of adipokines, including leptin and adiponectin [18]. As tumors progress, CAAs reorganize their actin cytoskeleton and acquire a fibroblast-like morphology by upregulating the expression of fibroblast-like biomarkers such as fibroblast activation protein (FAP), smooth muscle actin (a-SMA) and chondroitin sulfate proteoglycans [19]. Thus, CAAs may develop a more malignant phenotype than the original adipocytes, promoting OC proliferation, invasion, metastasis, immune escape and drug resistance through a lower immune barrier and the production of more aggressive adipokines in addition to other cytokines (**Figure 1**).

Adipokines and inflammatory cytokines derived from adipocytes

Adipocytes regulate several life activities through the secretion of cancer-associated adipokines, including leptin, adiponectin, visfatin, and resistin, as well as cancer-associated inflammatory cytokines, such as interleukin-6 (IL-6), monocyte chemotactic protein 1 (MCP-1), plasminogen activator inhibitor 1 (PAI-1) and tumor necrosis factor alpha (TNF-α). CAAs also produce metabolites, such as fatty acids (FAs) and diglycerides, which impact the fat distribution, insulin secretion, energy expenditure, and the inflammatory response [20]. The interaction between adipocytes and OC cells contributes positively to the proliferation, migration, invasion, and drug resistance of tumor cells [21]. In this study, we examine the impacts of leptin, adiponectin, visfatin, chemokines, MCP-1 and other crucial cytokines on in this crosstalk relationship. Targeting these cancer-associated adipokines and cytokines presents novel therapeutic possibilities for treating OC.

Leptin

Leptin is linked to the proliferation, migration, invasion and angiogenesis of tumors. A prior investigation revealed a significant increase in the expression of both leptin and its receptor in tissues affected by breast cancer compared to benign breast tissue and normal paracarcino-

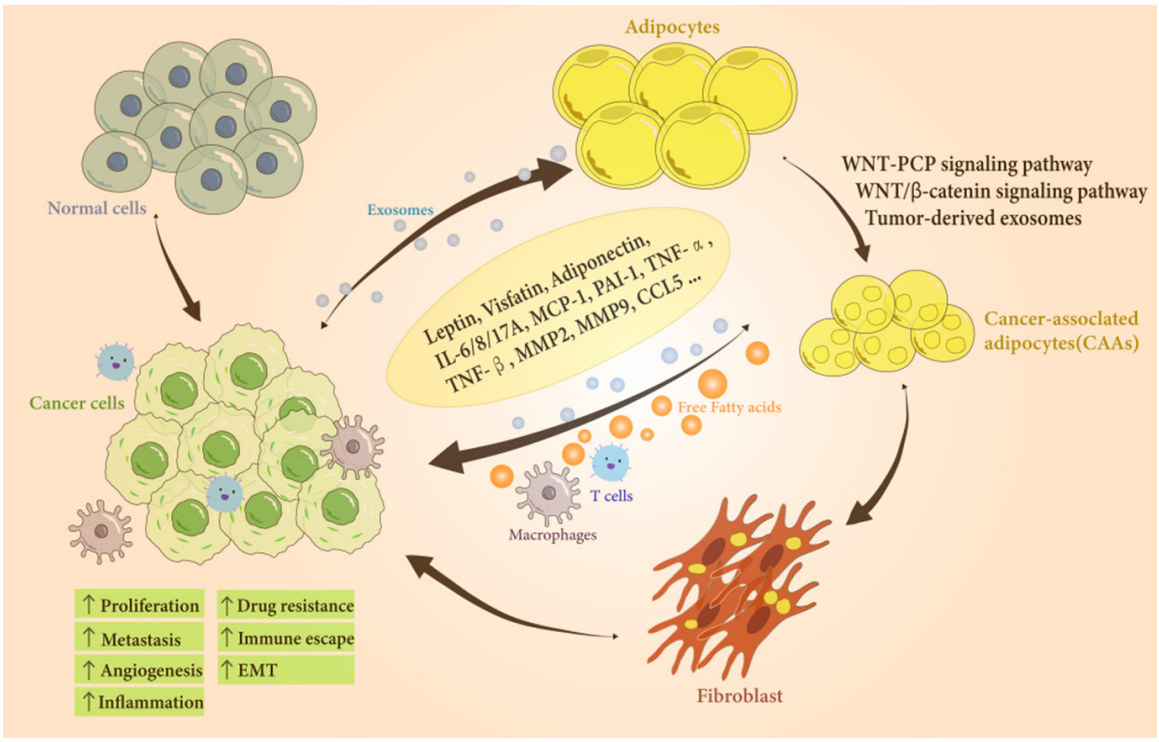

Figure 1. Interaction between adipocytes and ovarian cancer cells diagram. IL-6, interleukin-6; IL-8, interleukin-8; IL-17A, interleukin-17A; MCP-1, monocyte chemotactic protein 1; PAI-1, plasminogen activator inhibitor 1; TNF-α, tumor necrosis factor alpha; TNF-β, tumor necrosis factor beta; MMP2, matrix metalloproteinase 2; MMP9, matrix metalloproteinase 9; CCL5, C-C motif chemokine ligand 5; EMT, epithelial mesenchymal transition.

ma tissue. We also identified strong correlations between the expression levels of these genes and lymph node metastasis and Ki-67 expression [22, 23]. In HepG2 and MCF7 tumor cells, leptin can promote the phosphorylation of the adaptor protein phosphotyrosine interaction 1 (APPL1) in tumor cells, thereby enhancing tumor proliferation and migration [24]. Leptin increases the likelihood of obesity-associated cancers, particularly hormone-dependent tumors such as breast cancer, endometrial cancer, and ovarian cancer. In OC, leptin increases the expression of cyclin D1 and myeloid cell leukemia-1 (Mcl-1) by activating the methyl ethyl ketone (MEK)/extracellular regulated protein kinases 1/2 (ERK1/2) and PI3K/AKT signaling pathways, thereby inhibiting apoptosis and stimulating proliferation, which is associated with shorter survival of patients with malignant tumors [25]. Thus, leptin has the capacity to control various aspects of tumorigenesis and development through autocrine, endocrine and paracrine pathways, making it an essential target for the prevention and treatment of OC.

Visfatin

Visfatin is implicated in β-oxidation, the inflammatory pathway and the angiogenesis pathway. Additionally, visfatin was found to increase the invasiveness of glomus granulosa cells by increasing the expression of matrix metalloproteinase 2 (MMP2) while decreasing the levels of CLDN3 and CLDN4 [26]. A separate study revealed that visfatin enhances lipid accumulation and promotes tumor cell growth, proliferation and metastasis through the epidermal growth factor receptor (EGFR)/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/glycogen synthase kinase 3 beta (GSK3β)/sterol-regulatory element binding protein-1 (SREBP-1) signaling pathway [27]. Visfatin-inhibiting drugs can impede carbohydrate metabolism by blocking the glycolytic process in malignant tumor cells after the drugs have entered the cells, thereby promoting tumor cell apoptosis [28]. Moreover, silencing visfatin can also enhance the chemosensitivity to 5-FU through the SDF-1/CXCR4/Akt signaling pathway [29]. Therefore, further study of lipid-mediated cell plasticity will be conducive to the development

of better methods for the prevention and treatment of OC, especially in obese patients.

Resistin

The binding of resistin to its receptor triggers various signaling pathways, resulting in tumor cell proliferation, invasion, migration, drug resistance and the epithelial-mesenchymal transition (EMT). For instance, increased expression and secretion of resistin can stimulate prostate cancer cell proliferation by activating the PI3K/AKT signaling pathway [30]. Additionally, resistin stimulates the invasion and metastasis of lung adenocarcinoma cells by activating the Toll-like receptor 4 (TLR4)/Src/EGFR/PI3K/nuclear factor-κ-gene binding (NF-κB) signaling pathway and subsequently promotes tumor progression [31]. With respect to treatment resistance, resistin releases its epigenetic repression by DNA methyltransferases (DNMT1 and DNMT3a), increasing ABC transporter expression and drug efflux in multiple myeloma. Additionally, resistin can activate the adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR)/unc-51-like autophagy activating kinase 1 (ULK1) and c-Jun N-terminal kinase (JNK) signaling pathways to induce autophagy in tumor cells, resulting in drug resistance [32]. Resistin is closely linked to tumorigenesis and development. Its carcinogenic impact is mainly mediated by the induction of the EMT, which also affects the treatment and prognosis of tumors [33]. Therefore, it is currently being studied as a potential strategy for tumor treatment.

Adiponectin

Unlike most adipokines, adiponectin possesses distinct antitumor properties, including anti-inflammatory effects, cell proliferation inhibition, insulin resistance reduction, and apoptosis promotion. A recent study showed that adiponectin plays an important role in inhibiting tumor progression through its essential receptors, AdipoR1 and AdipoR2 [34]. Lehr S et al. discovered that adiponectin has the potential to inhibit tumor cell proliferation and encourage tumor cell apoptosis by activating the AMPK signaling pathway and inhibiting the PI3K/AKT signaling pathway [35]. Nevertheless, adiponectin can also stimulate the development of pancreatic cancer by enhancing the AMPK/NAD-dependent deacetylase sirtuin-1 (Sirt1)/PGC-1α signaling pathway [36]. In conclusion, adiponectin is an effective antitumor agent for a variety of tumors. It has shown therapeutic efficacy both as a standalone agent and as an adjuvant.

Estrogen

Adipocytes also produce high levels of the tumor-promoting hormone estrogen, especially in obese individuals [37]. Estrogen can enhance sympathetic tone in adipose tissue depots to varying degrees, either directly or by activating relevant receptors in adipocytes, to promote lipid deposition and function. Estrogen not only increases the risk of OC but also promotes tumor progression through its mitogenic capacity in the early stages of OC, and estrogen deficiency also leads to imbalances in glucose and lipid metabolism [38]. Interestingly, the two receptors of estrogen, ERα and ERβ, play completely opposite roles, which also provides different ideas for the treatment of tumors [39]. In ERα-positive OC, estrogen promotes the EMT pathway and induces a more malignant and invasive phenotype by activating the ERα/chemokine C-X-C-motif receptor 7 (CXCR7)/chemokine ligand 11 (CXCL11) signaling axis [40]. However, ERβ can inhibit the expression and activity of ERα, thus inducing cell apoptosis and reducing the proliferation and metastasis of OC [41]. Furthermore, high ERβ expression and individual sensitivity to platinum/taxane-based chemotherapy regimens are positively correlated in OC [42]. Furthermore, estrogen metabolites react with DNA to form estrogen DNA adducts, which are not only key factors in initiating the occurrence of OC but can also be used as early diagnostic markers for assessing the risks of OC and other hormone-dependent cancers [43].

IL-6/8/17A

The expression and secretion of the inflammatory cytokines IL-6/8/17A by adipocytes increase upon coculture with tumor cells, facilitating the infiltration of inflammatory cells and the progression of tumors. IL-6 promotes tumor cell migration and invasion through the ERK/STAT3 and Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling pathway [44]. IL-8 increases the expression of FABP4, aiding in the absorption of FAs by adipo-

cytes and facilitating the transport of OC cells to the greater omentum by regulating lipid metabolism [45]. IL-17A promotes FA uptake and utilization through the IL-17A/IL-17RA/p-STAT3/FABP4 signaling axis, leading to the rapid growth and metastasis of OC in an adipocyte-rich environment [46]. These inflammatory cytokines play crucial roles in tumorigenesis and tumor progression. Additionally, they bolster the resistance of OC to primary chemotherapy agents, namely, platinum and paclitaxel. Consequently, these cytokines could be potential targets for precision treatment of OC, but the specific mechanism requires further research.

MCP-1

Although previous research has suggested that MCP-1 production is involved in the host defense against tumors, recent studies have shown a positive correlation between MCP-1 levels, tumor-associated macrophage (TAM) infiltration, and tumor progression. Sun C et al. proposed that tumor cells preferentially migrate to the omentum, which is abundant in adipocytes, and that MCP-1 produced by these adipocytes plays an essential role in this migration process. On one hand, the recruitment of TAMs by MCP-1 modulates the immune microenvironment of tumors and contributes to the immune escape of tumor cells [47]. On the other hand, the specific binding of MCP-1 to its receptor CCR2 activates the PI3K/AKT/mTOR signaling pathway, leading to the expression of the downstream factors hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor-A (VEGF-A), which favor OC growth and extensive abdominal metastasis [48]. Currently, anti-MCP-1 antibodies or CCR-2 antagonists alone or in combination with other drugs have achieved some positive results in clinical trials for some tumors [49]. Therefore, a therapeutic strategy targeting MCP-1 and its associated signaling pathways is expected to be a therapeutic approach for preventing obesity-associated tumor progression.

PAI-1

PAI-1 is highly expressed in most cancers, including esophageal, gastric, and colorectal cancer, and is associated with a poor tumor prognosis [50]. PAI-1 can promote tumor angiogenesis and thereby lead to cutaneous angiosarcoma progression. By constructing a xenograft tumor model, Li Y et al. confirmed that PAI-1 promotes M2 macrophage polarization in colorectal cancer through the fibroblast growth factor receptor 2 (FGFR2)/PAI-1 signaling pathway, which then induces effective immunosuppression and promotes tumor progression [51]. Another study documented the noteworthy effect of PAI-1 on the regulation of immune checkpoints by promoting lysosomal degradation of programmed cell death ligand 1 (PD-L1). Thus, antagonizing PAI-1 expression and secretion in peritumoral adipocytes may provide a potential therapeutic target for tumor treatment. For example, the combination of a PAI-1 inhibitor and anti-PD-1 therapy was able to enhance the immune response and antitumor activity in xenograft tumor-bearing mice [52].

TNF-α

Although TNF-α has strong anti-inflammatory effects, it is widely acknowledged as an immunosuppressive cytokine. Multiple studies have shown that TNF-α can significantly facilitate tumor formation and cancer cell proliferation by upregulating the transcript levels of various inflammatory and chemical factors. Moreover, it promotes tumor cell migration and invasion by enhancing the metastatic phenotype [53]. In epithelial tumors, TNF-α can stimulate MMP secretion, which then induces an EMT program in epithelial tumor cells to enhance tumor migration, invasion, and metastasis [54]. Furthermore, Salomon BL. et al. reported that TNF-α also facilitates tumor progression by upregulating VEGF expression to promote tumor angiogenesis [55].

The metabolites related to CAAs primarily consist of FA and diacylglycerol. Compared with adipocytes from lean patients, adipocytes from obese patients supply more FAs to tumor cells. These free fatty acids can serve as a fuel source for cancer through mitochondrial fatty acid oxidation (FAO), which produces approximately twice the energy of glucose [56]. FAs are involved in the glucose uptake by various tumor cells, including OC cells. FAs can promote the growth and metastasis of malignant tumors by inducing the release of inflammatory factors and the recruitment of macrophages and lymphocytes to malignant tumor cells [57]. Furthermore, diacylglycerol is an endogenous

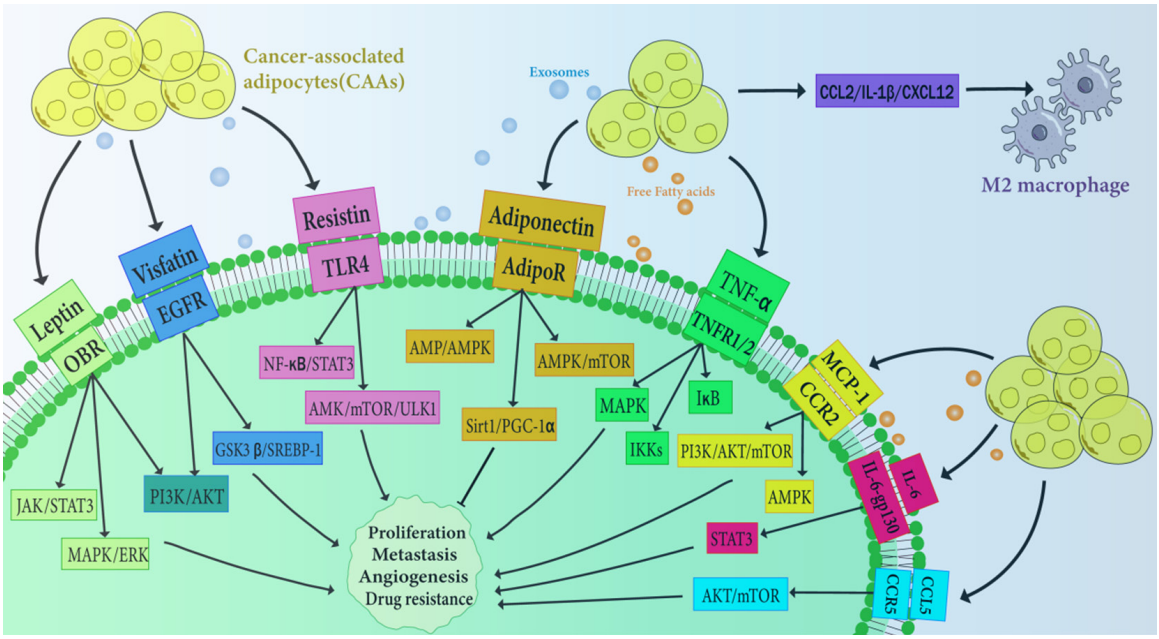

Figure 2. Adipokines derived from adipocytes impact signaling pathways governing ovarian cancer cell behaviour. CCL2, C-C motif chemokine ligand 2; CCL5, C-C motif chemokine ligand 5; IL-6, interleukin-6; IL-1β, interleukin-1 beta; CXCL12, chemokine (C-X-C motif) ligand 12; OBR, leptin receptor; EGFR, epidermal growth factor receptor; TLR4, toll-like receptor 4; TNFR, tumor necrosis factor receptor; CCR2, chemokine C-C-motif receptor 2; CCR5, chemokine C-C-motif receptor 5; JAK, Janus Kinase; STAT3, signal transducer and activator of transcription 3; MAPK, mitogen-activated protein kinase; ERK, extracellular regulated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, accredited kanban trainers; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; NF-κB, nuclear transcription factor kappa B; IKB, NF-kappa-B inhibitor; PGC-1α, peroxisome proliferator-activated receptor γ coactiva-tor-1 alpha; Sirt1, NAD-dependent deacetylase sirtuin-1; GSK3β, glycogen synthase kinase-3 beta; mTOR, mammalian target of rapamycin; SREBP-1, sterol-regulatory element binding proteins-1.

intermediate of fat metabolism in humans and has been shown to reduce visceral fat, inhibit weight gain and lower blood lipid levels [58]. Diacylglycerol can reduce programmed cell death, known as apoptosis, in malignant tumor cells by inhibiting the release of ceramide in the human body [59]. In summary, FAs and diglycerides, the relevant metabolites of CAAs, play important fuel roles in the efficient glycolytic reactions of tumor cells, providing the energy required for the synthesis of the cancer biomass, migration and invasion.

Numerous studies have revealed the mechanisms through which CAAs promote the development of OC cells (**Figure 2**). These mechanisms include their lipid storage and endocrine functions, as well as their ability to release hormones, inflammatory factors, and adipokines. On the other hand, signaling molecules produced by tumor cells can trigger the lipolysis of intratumor adipocytes and CAAs and even influence the entire global adipose tissue fat breakdown program within the body [60]. Tumor-derived TNF-α and IL-6 further lead to muscle wasting by inducing adipose atrophy, leading to cancer cachexia and compromising patients' quality of life and tolerance to antitumor drugs [61]. Blocking the interaction between tumor cells and CAAs may improve the treatment and prognosis of OC patients. Thus, inhibiting adipokines, inflammatory factors, and metabolites produced by adipocytes could constitute a novel therapeutic strategy.

Effects of CAAs on the biological behavior of ovarian cancer cells

The adipose tissue microenvironment (ATME) is composed of various cell types, such as adipocytes, stromal cells, immune cells, vascular endothelial cells and fibroblasts [9]. The adipocyte-rich TME is important for the proliferation, metastasis, immune escape, response to drugs and metabolic reprogramming of ovarian tumors.

Effects of CAAs on the proliferation and metastasis of OC

Tumor cells are capable of synthesizing most FAs for energy storage, protein synthesis, and the generation of signaling molecules required for various biological functions. However, endogenous lipids alone are insufficient to fuel tumor progression and survival. Therefore, tumors rely on adipocytes in the TME to acquire an additional abundant source of lipids. Adipose tissue is mainly divided into brown adipose tissue (BAT) and white adipose tissue (WAT) according to its location, morphology and function [62]. Among these tissues, WAT is characterized by single lipid droplets rich in triglycerides, which have high secretory activity in diseases such as tumors and obesity. Its core function is to store energy in the form of FAs, which affect, the metabolic processes of the system through the production of hormones and adipokines [63]. Research has validated that coculture of adipocytes and OC cells leads to an increase in the expression of FABP4, indicating increased lipolysis in omental adipocytes. This process promotes the spread of tumor cells [64]. Adipocytes not only serve as a source of energy for tumor cells but also release a plethora of dissimilar soluble factors that promote the proliferation, invasion, and chemotaxis of metastatic cells. Wang F et al. discovered that CCDC3 derived from adipocytes could enhance the tumorigenesis of epithelial ovarian cancer (EOC) through the Wnt/β-catenin signaling pathway [65]. Furthermore, Dai L et al. documented that the activation of adipocyte-induced SphK2 in EOC cells relies on ERK and that the inhibition of SphK2 significantly impedes adipocyte-induced cell proliferation [66]. Therefore, targeting adipocyte-produced cytokines such as CCDC3 and SphK2, which are considered hotspots for the treatment of tumors, is also a potential approach for OC treatment. In addition, CAA-derived lipid compounds can adapt to the rapid proliferation of tumor cells and cell signal transduction by accelerating the formation of cellular and organelle membranes [67].

Metastasis is a crucial manifestation of advanced OC. A study confirmed that fat cell-induced serine/threonine protein kinase 2 (SIK2) activation promotes the movement, migration, and transfer of OC cells by phosphorylating recombinant myosin light chain kinase (MYLK) in vitro and in vivo [68]. Furthermore, Wang C et al. discovered that SphK1 was overexpressed in retinal metastases of patients with EOC. SphK1 regulates the conversion of E/N-cadherin induced by adipose cells through Twist1, which is a crucial process in OC metastasis. This finding presents a novel target for the metastasis of epithelial cells in the ovaries [69]. Furthermore, the influence of dedifferentiated adipocytes on the proliferation and migration of OC cells was examined using both an in vitro coculture experimental model and an in vivo mouse model. Iyoshi S et al. reported that the coculture of OC cells with adipocytes facilitated peritoneal adipocyte dedifferentiation by activating the Wnt/β-catenin signaling pathway. Subsequently, these fibroblasts (O-ADFs) display tumor-promotion characteristics, as evidenced by increased proliferation and migration [70]. Current evidence indicates that adipocyte-derived cytokines play an essential role in cancer progression. Additionally, adipocyte-derived exosomes, which are extracellular vesicles arising from the kernel body, are also significant components of the adipose cancer interaction. Their paracrine and endocrine functions contribute to the progression and metastasis of primary tumors. In recent years, the treatment of OC with EVs, which have potential for use as a treatment option, has received increasing attention.

Effect of CAAs on immune escape of OC

OC is a solid tumor with a highly suppressive immune microenvironment. CAAs are not only enriched in the OC microenvironment but also associated with a poor patient prognosis. A substantial amount of data suggests that enhanced immune cell infiltration is linked to improved overall survival. One study revealed that CAAs-derived EVs transport SIRT1, which activates the CD24/recombinant sialic acid binding Ig like lectin-10 (Siglec-10) signaling pathway, encourages CD8+ T cells apoptosis to inhibit the immune response, and promotes OC tumorigenesis [71]. PD-L1 expression in CAAs prevents anti-PD-L1 antibodies from activating important antitumor functions of CD8+ T cells that help tumor cells escape the immune system [72]. The combined actions of adipocytes and immune cells affect invasive tumor cell growth in the omentum, which is a key reason

why most OC patients display widespread peritoneal metastasis. In addition to lymphocytes, a significant accumulation of monocytes occurs in the TME, and these cells differentiate into macrophages in adipose tissue in association with obesity [63]. These macrophages surround and ingest dead or dying adipocytes, forming crown-like structures (CLSs), a characteristic morphology of adipose tissue macrophages [73]. Macrophages can be divided into two major subgroups, M0 and M1 macrophages, which are associated with a positive prognosis, and M2 macrophages, which are associated with a negative prognosis [71]. CAA-derived EV-coated LINC01119 promotes M2 macrophage polarization and immune system evasion in 3D cell models cocultured with OC cells. The host components of the ovarian tumor microenvironment, particularly peritoneal mesothelial cells and adipocytes, produce Wnt5a, which promotes the adhesion, migration, and invasion of OC cells and peritoneal mesothelial cells, leading to extraperitoneal colonization. In a mouse xenograft tumor model, the deletion of Wnt5a increased the proportion of peritumoral cytotoxic T cells and M1 macrophages and decreased the expression of PD-L1, which contributed to tumor killing and immune clearance [74]. An in-depth understanding of the interaction mechanisms among adipocytes, tumor cells and immune cells will facilitate the development of specific antitumor drugs and will continue to drive the development of new antitumor treatments.

A recent study revealed that mesenchymal stem cells derived from adipose tissue next to tumors are vulnerable to dedifferentiation into multiple cancer-associated fibroblasts (CAFs) in the TME when cocultured with MDA-MB-231 or BT474 breast cancer cell. This group included the myofibroblast (myCAF) and inflammatory fibroblast (iCAF) subgroups. The myCAF phenotype contributes to extracellular matrix (ECM) remodeling, facilitating cancer cell migration and invasion, and promoting drug resistance. On the other hand, the iCAF phenotype is involved in immunosuppression and supports tumor growth in the TME [75]. During tumorigenesis and progression, CAFs generate and secrete a variety of cell growth factors, inflammatory factors, metabolites, enzymes, and ECM proteins, including collagen and proteoglycans. These substances stimulate tumor cell proliferation, migration, angiogenesis, metastatic phenotype, immune escape and the stemness of tumor stem cells [76, 77]. CAFs can increase the stiffness and thickness of the tumor extracellular matrix through the production of collagen, fibronectin and lamin. This process reduce blood vessel activity and decrease permeability to chemotherapeutic drugs, providing improved structural support for tumor migration. In addition to their analogous functions, CAAs and their evolved CAFs are implicated in multifaceted and dynamic metabolic reprogramming processes, which can alter the ECM under favorable circumstances. This process can affect tumor treatment and the patient prognosis.

Moreover, ferroptosis is a novel type of iron-dependent cell death characterized by the formation of lipid peroxides and the excessive accumulation of reactive oxygen species. The TME of the high-score group contained more immune cells, including activated CD4(+) T cells, activated CD8(+) T cells, macrophages, and stromal cells (adipocytes, epithelial cells and fibroblasts). When constructing a prognostic scoring system for OC patients, ferroptosis may impact the progression of OC through the mediation of tumor metastasis and immune patterns. You Y et al. confirmed four potentially sensitive drugs based on this prognostic score, namely, staurosporine, bleomycin B, DMOG and HG6-64-1, of which DMOG is considered a new targeted agent for the management of OC [78]. Therefore, elucidating the basic mechanisms of immune cells and the immune cascade driven by adipocytes is imperative to identify these cells as potentially profitable therapeutic targets.

Effect of CAAs on the drug resistance of OC

Resistance to platinum drugs in EOC is increasing at an alarming rate, with approximately 75% of patients developing chemotherapy resistance and experiencing tumor relapse. Adipocytes in the TME are dynamic cells, and their influence on resistance to antitumor therapies is receiving increasing attention. Mukherjee A et al. presented evidence that high expression of FABP4, which is derived from adipocytes in ovarian cancer cells, not only promotes metastasis but also mediates carboplatin resistance. Targeting FABP4 in ovarian cancer cells inhibit-

ed their ability to adapt and colonize the adipocyte-rich tumor microenvironment. Additionally, it increased the sensitivity of tumor cells to carboplatin both in vitro and in vivo [79]. Conversely, Zhou S et al. reported that the adipocyte-secreted protein angiopoietin like protein 4 (ANGPTL4) activates the c-myc/NF-κB signaling pathway, which in turn stimulates the expression of the antiapoptotic protein Bcl-xL and members of the ABC transporter family, including ABCB1, ABCC1, and ABCG2. Finally, OC resistance to carboplatin was induced [80]. Another study revealed that arachidonic acid (AA) secreted by adipocytes obstructs cisplatin-induced apoptosis by activating the AKT signaling pathway, thereby augmenting the resistance of ovarian cancer cells to chemotherapy drugs. Consequently, hindering AA production by adipocytes or obstructing their antiapoptotic function may inhibit chemotherapy resistance in patients diagnosed with EOC [81]. For patients with advanced OC requiring high-dose hormone shock therapy, adipokines derived from adipocytes have the potential to decrease the antitumor efficacy of related hormone therapy drugs. A study conducted by Bougaret L and his colleagues showed that adipose-derived leptin, IL-6 and TNF-α were able to diminish the antiproliferative effects of 4-OH-Tx, the primary active metabolite of the antiestrogenic medication tamoxifen, in both 3D and coculture models of MCF7 tumor cells [82].

Several studies have confirmed that adipocytes not only stimulate relevant molecular pathways through cytokines, chemokines and hormones but also affect the TME by liberating EVs that contain miRNAs, which subsequently affect the drug resistance of OC cells and ultimately result in disparities in patient survival. On the one hand, the levels of miR-21 are markedly higher in EVs and tissue lysates collected from CAAs than in those collected from OC cells. MiR-21 hinders the apoptosis of OC cells and confers chemoresistance by binding to APAF1 [83]. On the other hand, miR-181 enhances the sensitivity of OC cells to chemotherapy drugs by suppressing MEST through the Wnt/β-catenin signaling pathway [84]. MiR-146 targets LAMC2, decreases its expression, and activates the PI3K/AKT signaling pathway, thereby inhibiting chemotherapy resistance [85]. MiR-424 decreases VEGF levels by inhibiting the myeloblastosis (MYB) signaling pathway, consequently diminishing the proliferation and angiogenic capability of tumor cells [86]. Hence, as a crucial factor and mediator of intercellular communication, miRNA-based regulation is closely associated with adipocyte-secreted factors in OC progression and metastasis. Furthermore, EVs secreted by ADSCs have the potential to serve as effective carriers for drugs and bioactive molecules, including miRNAs, siRNAs, long noncoding RNAs (lncRNAs), and cytokines. These EVs could result in lower minimum effective doses, reduced systemic toxicity, and protection of the drug from premature degradation. Thus, targeting EV communication may also be a promising new strategy for overcoming drug resistance during tumor treatment.

Another form of tumor therapy, oncolytic virus (OV) therapy, has been found to be more effective with the addition of FA transporter inhibitors. Additionally, secreted products in adipocyte-conditioned media significantly reduced OV-driven cell death and viral infection. Abera Surendran et al. discovered that these inhibitors can sensitize breast cancer and ovarian cancer cells to OV therapy by reducing the lipid content within the TME. These findings suggest that combination strategies utilizing virotherapy and FA transporter inhibitors have great clinical potential for overcoming OV resistance caused by adipocytes [87].

Effect of CAAs on the metabolism of OC

Tumor cells can acquire nutrients from an environment that is depleted of nutrients. They utilize these nutrients to preserve their transformed state, accumulate biomass, and facilitate cell proliferation [88]. The Warburg effect was first proposed in the 1920s. Tumor cells obtain large amounts of ATP through a series of molecular mechanisms to impair aerobic respiration and perform efficient glycolysis, which can create an environment suitable for the survival of tumor cells and help them evade the normal apoptosis program and promote tumor proliferation and metastasis [89]. Since then, metabolic reprogramming has emerged as a hallmark of tumor cells. Numerous recent studies have focused on differential alterations in glucose, lipid, and amino acid metabolism occurring in key metabolic pathways associated with tumors to explore novel therapeutic strategies to counteract malignancies, including OC.

Ongoing interactions between OC cells and adipocytes result in metabolic competition and symbiosis, leading to oncogenic metabolic reprogramming of tumor cells and adjacent adipocytes. Glucose metabolism in tumor cells is altered through aerobic glycolysis, which fulfills the energy needs of tumor cells in the cytoplasm. Pyruvate derived from glycolysis is continuously transformed into lactic acid. This process prevents glucose from entering the mitochondria for oxidative phosphorylation (OXPHOS) [90]. In general, lactic acid levels are high in solid tumors. A transmembrane protein associated with a poor tumor prognosis, the monocarboxylate transporter (MCT), mediates the transport of a variety of monocarboxylate salts, including lactic acid, ketones and pyruvate. In primary mammary-derived adipocytes, the overexpression of MCT1 and MCT2 is responsible for lactate uptake for additional energy, whereas MCT4 promotes lactate efflux to maintain a stable intracellular pH. These proteins are involved in the proliferation, invasion, and migration of tumor cells and are closely related to the tumor prognosis. Moreover, MCT1 is involved in the uptake of monocarbylate to generate more ATP for tumor utilization [91].

In addition to glucose metabolism, the metabolism of FAs (including both synthesis and oxidation) plays a significant role in the metabolic phenotype of OC. Hypoxia in the adipose-tumor microenvironment is the driving force for fat uptake by OC cells. OC cells stimulate adipocyte lipolysis and the subsequent massive uptake and utilization of FAs from surrounding adipose tissue. Notably, FAs can be used as a fuel source for tumors through mitochondrial fatty acid oxidation (FAO), which produces approximately twice as much energy as glucose [92]. On the one hand, FAs enter tumor cells through specific fatty acid receptors and binding proteins, such as CD36 and fatty acid transport protein 1 (FATP1). FAs are subsequently used to synthesize membrane structures, for energy metabolism (β-oxidation), or for lipid-derived cell signaling molecules. On the other hand, FAs can be used as a structural unit of newly synthesized membrane phospholipids, and the uptake of FAs by tumor cells can increase the content of saturated FAs in the cell membrane and subsequently reduce tumor cell apoptosis and drug absorption [93]. In another potential pathway, omental adipocytes induce calcium-mediated SIK2 activation in OC cells, which in turn increases FA and cholesterol synthesis through the PI3K/AKT and sterol regulatory element binding protein-1c (SREP-1c)/fatty acid synthase (FASN) and SREB2/HMGCR signaling pathways, thereby promoting tumor cell proliferation and metastasis [94, 95]. Ladanyi A et al. reported that coculture of EOC cells with primary human omental adipocytes resulted in high plasma membrane expression of the FA receptor CD36, which promoted exogenous FA uptake and increased intracellular reactive oxygen species (ROS) levels. Targeting stromal tumor metabolism by inhibiting CD36 may be an effective strategy for the treatment of EOC metastasis [96]. Thus, FA metabolism confers a survival advantage to OC cells, and blocking fatty acid synthesis inhibits tumor growth and survival, making treatments targeting FA metabolism a promising antitumor strategy.

Furthermore, recent research into amino acids in the TME has indicated that adipose stromal cells within the TME can also participate in a symbiotic metabolic process with tumor cells through arginine metabolism. The manipulation of the arginine metabolic pathway has the potential to impact tumor proliferation, invasion, and apoptosis [97]. Glutamine is both the most abundant amino acid in plasma and an immune metabolic regulator in WAT. Research has showed that administering glutamine in vitro and in vivo results in reduced proinflammatory gene expression and protein levels in adipocytes, as well as decreased macrophage infiltration in WAT [98]. Adipocytes in the TME re-establish the metabolism of glutamine, from its breakdown to its synthesis, to supply more abundant nutrients for tumors, and they play a pivotal role in the metabolism of tumor cells [99].

Notably, lipoautophagy (autophagic degradation of lipids), another catabolic pathway that has recently been intensively studied, plays a role in the release of free fatty acids. These FAs can be used to construct cell membranes or are catabolized through β-oxidation to meet the increased energy and biosynthetic demands of tumor growth [100]. The TME triggers the AMPK pathway by regulating nutrients, oxygen, growth factors and soluble factors, which regulates autophagy in OC. This process may

cause tumor cells to enter a nonproliferative quiescent state, protecting them from toxic damage while still retaining their stem cell-like properties [101]. Further evidence is needed to elucidate the perturbations of lipophagy in the TME, to fully understand its role in the development and progression of OC, and to determine its potential as a novel therapeutic approach for this malignancy [102].

Given the role of adipocytes in nutrient metabolism and energy expenditure and their crosstalk with tumor cells, targeted metabolic research on adipocytes provides a potential precision therapeutic strategy for tumor treatment. The potential efficacy of some metabolic drugs currently in clinical trials, such as drugs targeting FASN, drugs targeting CD36, and PPAR-γ antagonists, are also highlighted. Thus, blockade of adipocyte-derived lipid uptake or lipid-related pathways within tumor cells by single agents or combination chemotherapy may prove to be an effective strategy for tumors that grow in an adipocyte-rich tumor microenvironment.

Mechanism of action of CAAs in the biological behavior of ovarian cancer

This article details how adipocytes contribute to OC proliferation, metastasis, immune escape, chemotherapy resistance, and metabolic reprogramming. Based on the existing evidence, we established that adipocytes impact OC progression through four distinct mechanisms.

1) Adipocytes can secrete adipokines, nutrients, miRNAs and other bioactive molecules into the TME to promote tumor cell proliferation and invasion. A prime example is leptin, which is secreted from WAT into the ATME. Leptin acts on the JAK-2/STAT, PI3K/AKT-1 and MAPK/ERK1/2 signaling pathways and exerts synergistic effects on a variety of different oncogenes, cytokines and growth factors [103, 104].

2) Adipocytes accelerate the immune escape of tumors and increase the resistance of OC to chemotherapy and immunotherapy by regulating immune cells within the TME, including lymphocytes, mononuclear cells/macrophages and mast cells. For example, adipocytes secrete chemokines into the TME, enabling them to recruit other inflammatory cells. Infiltrating inflammatory cells, such as mast cells, can generate a variety of proteases, including cathepsin S, which can lead to tumor progression and resistance to chemotherapy [105, 106].

3) Adipocytes can regulate vascular endothelial cells, thereby promoting tumor angiogenesis and accelerating tumor progression. On the one hand, adipocytes in the ATME strongly support tumor growth and increase angiogenesis by releasing specific molecules directly into tumor cells. On the other hand, adipocytes recruit and activate macrophages through the CCL2/IL-1β/CXCL12 signaling pathway, which in turn promotes interstitial vascularization and angiogenesis [107, 108].

4) Adipocytes can modify the ECM structure, which is characterized by a high degree of fibrosis in the ATME, and thereby influence the biological behavior of tumors. An abundant profibroproliferative response can be observed in tumor areas enriched in adipocytes or located near adipose tissue, and the abnormal deposition of fibrous tissue can cause tissue stiffness, impeding blood flow and reducing the permeability of chemotherapy drugs [109, 110].

The connection between adipocytes in the TME of OC and tumor cells is so intimate that adipocytes undergoing a series of secretory and metabolic transitions have been renamed CAAs. Understanding the precise mechanisms by which CAAs affect tumor cell biological behavior is crucial for identifying potential therapeutic targets and tumor immune escape for current OC therapies, and a variety of biological mechanisms involved have been identified through studies of in vitro and animal models.

CAAs as a therapeutic targets for ovarian cancer and their clinical application potential

The complexity of current OC treatments hampers the implementation and advancement of therapeutic approaches. The majority of patients with OC will still relapse after initial treatment with surgery combined with chemotherapy. The therapeutic efficacy of OC treatment is mainly limited by chemotherapy resistance and a lack of targeted therapy. Among them, chemotherapy resistance induced by adipocytes

surrounding tumors has been documented by numerous studies. According to clinical studies, combination therapy, including cytotoxic drugs, targeted therapies, and lipid metabolism inhibitors, has proven to be more effective in tumor treatment. Several mechanisms indicate that therapeutic pathways directed toward adipocytes may prove useful in the treatment of OC.

Targeting the lipid supply

The supply of FAs to tumor cells is restricted to reduce their sources of energy production, thereby inhibiting tumor growth and progression. Drugs targeting FASN and fatty acid transporters can impact the production, transport, and utilization of lipids both in vivo and in vitro. For instance, inhibitors of CD36 (also known as a FA transport protein) are effective in decreasing microector-derived FA uptake by OC cells, thereby restraining the proliferation, invasion, and migration mediated by adipocytes [96]. Treatment with an MCT1 inhibitor targeting another FA transporter is effective at reducing tumor growth and increasing the intratumoral lactate content [111]. Furthermore, the inhibition of lipoautophagy prevents the growth-promoting effect of adipocytes and reduces the release of FAs and the ability of cancer cells to utilize FAs [100].

Targeting CAA-derived soluble factors

Targeting adipocyte-derived soluble factors that confer platinum resistance increases tumor cell apoptosis and drug efflux. We have previously shown that adipocyte-secreted cytokines such as FABP4, ANGPTL4 and AA induce OC resistance to platinum by activating their respective signaling pathways to stimulate the expression of antiapoptotic proteins and transporters. Maraviroc (a CCR5 inhibitor approved by the FDA) can block the recruitment and polarization of TAMs via the CCL5 axis, thereby inhibiting the proliferation and metastasis of tumor cells and improving the overall survival of patients [112]. Therapeutic strategies targeting CAA secretion can improve the sensitivity of tumor cells to drugs, reduce the inflammatory response in the TME, change the immunosuppressive state of the body, and ultimately affect the occurrence, progression and treatment resistance of OC.

Targeting lipid-derived EVs

MiRNA replacement therapy targeting EVs can reduce the minimum effective dose and systemic toxicity of drugs. Adipose tissue-derived EVs contain miRNAs, siRNAs, transcription factors, proteins and lipids, and these substances are involved in the regulation of cell communication and the modulation of cell biology. MiRNA expression is altered in ovarian cancer through a mechanism that not only upregulates proapoptotic molecules (BCL-2-associated X protein (BAX), recombinant caspase 9 (CASP9) and CASP3) but also downregulates the antiapoptotic protein B-cell lymphoma 2 (BCL2), which can function as either an oncogene or a tumor suppressor gene [113]. Therefore, EVs secreted by adipocytes are expected to be good carriers of drugs or bioactive molecules for the treatment of OC, which will be further confirmed in future clinical trials.

Targeting lipid metabolism

Lipid metabolism inhibitors are sensitive drugs that target tumor cells and angiogenesis. Bevacizumab and other antiangiogenic drugs are widely used in comprehensive clinical tumor treatment, mainly to inhibit tumor growth and metastasis by interfering with the supply of nutrients to the tumor. However, these drugs reduce the tumor vascular density and lead to tissue hypoxia. Hypoxia triggers the lipolysis of tumor-infiltrating CAAs and peritumoral CAAs, resulting in excess FAs. Hypoxia also upregulates the expression levels of fatty acid translocase or its receptor CD36 in tumor cells to increase FA uptake. Within tumor cells, FAs are metabolized through the β-oxidative pathway to produce ATP, which supports tumor cell proliferation and migration. These mechanisms partially explain how CAAs promote resistance to antiangiogenic drugs, and thus the combination of lipid metabolism inhibitors and targeted antiangiogenic therapies reduces OC resistance and benefits OC treatment and the prognosis. The potential efficacy of several drugs that target lipid metabolism and are currently undergoing clinical trials is also being highlighted. Aspirin alters the metabolomics and FA composition of 3t3-L1 adipocytes by inhibiting lipogenesis, oxidative stress, neoplastic formation, and obesity-related inflammatory responses, ultimately inhibiting tumor cell growth and metastasis [114]. An adipocyte-rich microenvi-

ronment promotes chemoresistance in EOC by upregulating the PPAR-γ/ABCG2 signaling pathway. In vitro and in vivo experiments in mice have shown that the chemotherapeutic effect on OC cells can be improved to a certain extent by PPAR-γ inhibition. However, due to species heterogeneity, further explorations are needed before PPAR-γ inhibitons can be used in the clinic [115].

Targeting the formation of CAAs

In addition, drugs targeting the formation of CAAs can be developed. For instance, metformin and epigallocatechin-3-gallate (EGCG) can inhibit the differentiation of ADSCs into adipocytes, thereby reducing the formation of CAAs and inhibiting the proliferation and invasion of tumor cells [116, 117].

Interestingly, although ovarian epithelial carcinoma is moderately sensitive to radiotherapy, its particular biological characteristics make it susceptible to widespread pelvic and abdominal metastases. Therefore, radiotherapy is not usually used for clinical OC. However, the interaction between adipose tissue and tumor cells undoubtedly amplifies the oxidative stress response, which subsequently diminishes the presence of free oxygen radicals, resulting in resistance to radiation therapy [118]. For example, adipocyte-derived cytokines have been shown to stimulate malignant tumor cells to produce high levels of IL-6, thereby protecting tumor cells from radiotherapy [119].

Although drugs have made significant contributions to OC treatment, drug resistance and a lack of targeted therapy have greatly reduced the treatment efficacy, shortened patient survival, and impaired the quality of life of OC patients. Traditional treatment strategies for OC have focused mainly on the tumor cells themselves, but with the growing interest in the TME, an increasing number of treatment strategies are focused on the stromal cells in the TME, such as adipocytes. Most obese patients have inflammatory adipose tissue that resembles chronic damage, and such fat depots can be a rich source of proinflammatory mediators [120]. In this environment, the influx of immune cells (including macrophages and lymphocytes), the production of proinflammatory mediators and growth factors, tissue remodeling, and angiogenesis are used to maintain the inflammatory microenvironment and promote tumor growth and metastasis [121]. OC grows in anatomical sites rich in adipose tissue, and tumor invasion promotes the dedifferentiation of adipocytes to form CAAs. Subsequently, CAAs acquire a fibroblast-like phenotype and promote the implantation and metastasis of ovarian cancer cells by secreting large amounts of proteases and cytokines (including IL-6 and IL-8) [64]. Moreover, adipocyte-rich tissue can also provide tumor cells with a rich source of lipids for rapid tumor growth. Therefore, when administered either as a single agent or in combination with standard chemotherapy regimens, treatments blocking adipocyte-derived lipid uptake or reprogramming lipid metabolism in cancer cells may prove to be effective strategies to trest obesity-related tumors (**Table 1**). Finally, adipose inflammation is a reversible process, and the development of noninvasive methods to detect fat health, including blood-based biomarker signatures or radiographic techniques can assess the WAT inflammatory status and help to improve the treatment efficacy and quality of life of OC patients.

Conclusion

Ovarian cancer is one of the most challenging gynecological tumors, with a high risk of metastasis, an extremely high recurrence rate and an alarming increase in resistance to chemotherapeutic drugs. Recently, an increasing number of investigations have used adipocytes as an entry point for OC treatment and have probed the vast potential of adipocyte-targeted therapy in both in vitro experiments and clinical trials. In general, the mechanisms of action of adipocyte-derived adipokines, metabolic reprogramming, ECM remodeling, miRNAs and immune cell regulation in the occurrence, development and treatment of OC should be highlighted. Previously, we summarized the progress of research on the role of adipocytes in OC, particularly how CAAs can significantly influence the biological behavior and therapeutic prognosis of OC. Moreover, this study highlights the potential to translate CAA-related therapeutic targets in current preclinical OC models into clinical applications. Current studies have shown that tumor cells and adipocytes have more obvious clinical relevance in obese patients and may weaken the therapeu-

Table 1. Potential therapeutic targets of CAAs in ovarian cancer

Strategy	Targets and drugs	Preclinical and clinical effects	Reference
Targeting lipid supply	Inhibitor of CD36	Reduce FA uptake by tumor cells and inhibit adipocyte-mediated proliferation and invasion	[96]
	FASN inhibition	Reduce FA generation and the energy utilization of tumor cells	[122]
	MCT1 inhibition	Reduce tumor growth and increase intra-tumor lactate	[111]
	Autophagy inhibition	Reduce FA release and attenuate the ability of tumor cells to utilize FAs	[123]
Targeting CAAs-derived soluble factors	Monoclonal antibody against VEGF-A	Inhibit the proliferation, angiogenesis and metastasis	[124]
	Inhibitor of FABP4	Reduce the ability of tumor cells to adapt to and colonize adipocyte--rich TME and promote the sensitivity to carboplatin	[79]
	Inhibitor of ANGPTL4	Promote the sensitivity to chemotherapy	[80]
	Inhibitor of AA	Promote cisplatin-induced apoptosis of tumor cells	[81]
	Inhibitor of CCR5 (Maraviroc)	Reduce the recruitment and polarization of TAMs, thereby inhibit tumor cell growth and metastasis	[125]
	Thymoquinone	Reduce the pro-inflammatory factors produced by CAAs such as IL-6 and IL-1β, thereby prevente the progression of tumor cells	[126]
Targeting lipid-derived EVs	miR-21	Inhibit the apoptosis and chemoresistance of ovarian cancer cell	[83]
	miR-181	Increase the sensitivity to chemotherapy	[84]
	miR-424	Reduce the proliferation and angiogenesis of tumor cells	[86]
Targeting lipid metabolism	PPAR-γ inhibiton (GW9662)	Promote tumor cell apoptosis and improve the effect of chemotherapy	[115]
	Aspirin	Alter the metabolomic and FA composition of adipocytes and inhibit tumor cell growth and metastasis	[127]
Targeting the formation of CAAs	Metformin	Inhibit the differentiation of ADSCs into adipocytes, thereby inhibit the proliferation and invasion of tumor cells	[128]
	Epigallocatechin-3-gallate (EGCG)	Inhibit the differentiation of ADSC into adipocytes, thereby prevent the invasive phenotype of tumor cells	[129]

FASN, fatty acid synthase; MCT1, monocarboxylate transporter 1; VEGF-A, vascular endothelial growth factor A; FABP4, fatty acid binding protein 4; ANGPTL4, angiopoietin like protein 4; AA, arachidonic acid; CCR5, chemokine C-C-motif receptor 5; PPAR-γ, peroxisome proliferator-activated receptor-γ; FAs, fatty acids; EVs, extracellular vesicles; ADSCs, adipose-derived stem/stromal cells.

tic effect of cancer therapy. Therefore, direct lifestyle interventions, such as diet and exercise, along with medical therapy may be the simplest and most effective strategies for such obese patients.

In the future, targeting adipocyte secretions, metabolites and lipid transport pathways will improve the efficacy of current OC treatments. Clinical studies have shown that while antitumor therapy with cytotoxic drugs, focused on the inflammatory state of adipose tissue, combined with lipid metabolism inhibitors and antiangiogenic drugs can effectively improve the efficacy of tumor therapy and prolong survival. Despite recent advances in adipocyte research, some unanswered questions remain. For example, the true synergistic effect of related drugs targeting adipocytes, such as FASN inhibitors and CD36 agonists, needs to be evaluated in further studies. In addition, the wide use of EV treatment technology also has difficulties that have not yet been overcome, such as the low loading efficiency of exogenous methods and difficulties in isolating EVs using endogenous methods. Further research is needed to determine the safety and efficacy of this therapy. At present, in-depth research into the crosstalk between adipocytes and OC cells and the study of adipocytes as potential therapeutic targets for OC are the joint efforts of several research laboratories around the world. An increasing number of ovarian cancer patients will likely benefit from these studies in the near future.

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Address correspondence to: Wenlin Xu, Department of Central Laboratory, The Fourth Affiliated Hospital of Jiangsu University, Zhenjiang 212000, Jiangsu, China. E-mail: xuwenlin0806@163.com

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