Multi-faceted role of cancer-associated adipocytes in the tumor microenvironment (Review)

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Abstract. Adipocytes are a type of stromal cell found in numerous different tissues that serve an active role in the tumor microenvironment. Cancer-associated adipocytes (CAAs) display a malignant phenotype and are found at the invasive tumor front, which mediates the crosstalk network between adipocytes (the precursor cells that will become cancer-associated adipocytes in the future) and cancer cells. The present review covers the mechanisms of adipocytes in the development of cancer, including metabolic reprogramming, chemotherapy resistance and adipokine regulation. Furthermore, the potential mechanisms involved in the adipocyte-cancer cell cycle in various types of cancer, including breast, ovarian, colon and rectal cancer, are discussed. Deciphering the complex network of CAA-cancer cell crosstalk will provide insights into tumor biology and optimize therapeutic strategies.

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Abbreviations: CAA, cancer-associated adipocyte; TME, tumor microenvironment; FABP, fatty acid-binding protein; IL, interleukin; MMP, matrix metalloproteinase; AT, adipose tissue; WAT, white adipose tissue; CAF, cancer-associated fibroblast; CCL, chemokine (C-C motif) ligand; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor; CRC, colorectal cancer; CCL-2, monocyte chemotactic protein 1; iNOS, inducible nitric oxide synthase; NO, nitric oxide; COX-2, cyclooxygenase-2; PPAR, peroxisome proliferator-activated receptor; FXR, farnesoid X receptor; BC, breast cancer; ECM, extracellular matrix; miR, microRNA; ATGL, adipose triglyceride lipase; CPT1A, carnitine palmitoyltransferase 1A; FATP1, fatty acid transporter-1; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; FAO, fatty acid oxidation; ATX, autotoxin; LPA, lysophosphatidic acid; AAD, antiangiogenic drug; HCC, hepatocellular carcinoma; FGF2: fibroblast growth factor 2; OBR, leptin receptor; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor-κB; AMPK, adenosine 5'-monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; TNBC, triple-negative BC; HER2, human epidermal growth factor receptor-2; CSC, cancer stem cell

Key words: CAA, metabolic reprogramming, chemotherapy resistance, adipokines, TME

1. Introduction

Tumor initiation and development depend on epithelial tissue and are closely associated with the surrounding tumor microenvironment (TME). Although no consensus has been reached concerning the definition of the TME, which is mainly composed of tumor cells, peripheral immune and inflammatory cells, tumor-related fibroblasts, peripheral interstitial tissue, microvessels and various cytokines and chemokines, it has become an important research focus to understand tumor development and to identify target for cancer treatment (1). Metabolic transformation is not only a sign of cancer, but also a key goal of cancer treatment. Due to the influence of cancer cells, the physiological characteristics of the TME (such as metabolism, secretion and immunity, amongst others) are no longer regulated by the body, which has a far-reaching impact on the progress of cancer. Remodeling of the TME has therefore become a cancer treatment strategy. However, how changes in the TME metabolic levels affect cancer metabolism and behavior remains unclear (2,3). Moreover, whether adipocytes (cells abundant in the TME) play a key role in the malignant progression of tumors remains to be determined. Considering the relationship between tumor progression and obesity, adipocytes are considered to be essential components of the TME (4). Currently, from the available *in vitro*, *in vivo* and clinical data, it can be demonstrated that the characteristics of adipocyte-derived factors change during tumor progression and tumor cells can also significantly affect the surrounding adipocytes. When peritumoral adipocytes display an altered phenotype and specific biological features (such as the decrease

in differentiation markers of mature adipocytes, production of a large number of fat-derived factors and the promotion of the metabolic reprogramming of cancer cells), they are termed cancer-associated adipocytes (CAAs) (5). CAAs are considered to serve an important role in the TME. Previous studies reported that adipocytes co-cultivated with cancer cells exhibited considerable morphological and functional alterations, including reduced lipid content and decreased adipocyte markers, such as adiponectin, leptin and fatty acid-binding protein (FABP)2 (6-8). Overexpression of interleukin (IL)-6, IL-1 and matrix metalloproteinase (MMP)-11 is also detected in activated adipocytes, which are also referred to as CAAs. Notably, in a tumor subset, growth and metastasis predominantly occur adjacent to adipocytes, for example, in breast cancer (BC), or at anatomical sites where cancer cells are close to the adipose tissue (AT), including in gastric, colorectal and ovarian cancer (9). Adipocytes participate in a highly complex inflammatory cycle that is regulated by tumor cells to promote tumor development. Moreover, the malignant functions of CAAs may amplify this cycle and therefore CAAs may serve as an obstacle to tumor treatment. A previous study has demonstrated that tumor drug resistance is an important driver of disease progression and could be a potential target for new therapies. The role of adipocytes in tumor drug resistance has been overlooked. CAAs cause drug resistance in oncological treatments, including chemotherapy, radiotherapy, hormone therapy and immunotherapy, which may lead to the persistence of tumor remnants and increase the risk of tumor recurrence (8). However, to the best of our knowledge the role of CAAs and how they evolve from adipocytes during tumor progression has previously not been described in detail. The present review has focused on the adipocyte-cancer cell circle in terms of metabolism, adipokines and drug resistance. The potential mechanisms underlying the dynamic communication between CAAs and numerous types of cancer, including BC, ovarian cancer and colorectal cancer (CRC), especially in the co-occurrence of obesity, which may result in neoteric therapy, have also been investigated.

2. Mature adipocytes and CAAs

AT comprises a highly complex and heterogeneous group of cellular components, mostly consisting of adipocytes. There are also numerous other types of stromal cells in AT, including endothelial cells, pericytes, macrophages and adipocyte progenitor cells. Both adipocytes and stromal vascular cells in AT contribute with several other factors towards tumor growth and maintenance (10-12). AT is an important and complex tissue that regulates energy balance and is distributed in almost all compartments of the human body. Histologically, there are three main types of AT: i) White AT (WAT), which accounts for >95% of the fat mass; ii) brown AT, which accounts for 1-2% of the fat mass; and iii) beige AT, which is difficult to quantify as it is scattered under the skin near the spine and clavicle in adults and cannot be taken out as a whole. WAT is the most dynamic AT in the human body, accounting for 2-70% of the body weight (13). Mature adipocytes are the main cell type in WAT, containing a small number of mitochondria (14). Mature adipocytes function by secreting various adipocytokines, and are characterized by a round shape with only one large lipid droplet (15). Compared with mature adipocytes, CAAs possess an irregular morphology, with small lipid droplets and a small volume. Furthermore, tumor-associated adipocytes usually have some changes (such as differentiation markers), as later described. Following lipolysis, differentiation markers of mature adipocytes decrease, such as adipocyte p2 and FABP4 (16,17). In the presence of cancer cells, especially at the tumor invasive front, CAAs generate fibroblast-like cells named adipocyte-derived fibroblasts after undergoing a process via which adipocytes decompose their lipids into glycerol and free fatty acids, and adopting a phenotypic change. These adipocyte-derived fibroblasts, as part of the cancer-associated fibroblast (CAF) population, are also involved in the malignant progression of tumors. It has also been indicated that CAAs may represent an intermediate form through which CAFs can arise (18). Moreover, CAAs have also been found to produce a number of adipose-derived factors via endocrine and paracrine signaling pathways, including chemokine (C-C motif) ligand (CCL)2, CCL5, IL-6, tumor necrosis factor α (TNFα), vascular endothelial growth factor (VEGF) and leptin; however, lower levels of adiponectin are produced (5,6). In terms of metabolic changes, CAAs promote numerous catabolic processes releasing high-energy metabolites, including lactic acid, pyruvic acid, free fatty acids and ketone bodies (5). Furthermore, CAAs provide sufficient energy for cancer cells by secreting exogenous fatty acids, leading to the metabolic reprogramming of cancer cells (19). Tumor cell-derived signaling molecules induce the lipolysis of adipocytes and promote the evolution of adipocytes to CAAs (20). Fig. 1 displays the complex relationship among tumors, adipocytes and CAAs. Therefore, CAAs are thought to serve a paramount role in tumor invasion and progression via the endocrine and paracrine signaling pathways.

3. Distinctive role of CAAs in different types of cancer

CAAs in CRC. Obesity and CRC are both global health issues and epidemiological data has demonstrated that obesity is positively correlated with CRC (21). Obesity serves a direct and independent role in the development of CRC. Previous studies have reported that cancer cells can increase carnitine palmitoyltransferase 1A (CPT1A) expression by interacting with CAAs, which in turn upregulates mitochondrial fatty acid oxidation and enables cancer cells to tolerate a hypoxic environment (21,22). Furthermore, crosstalk between tumor resident adipocytes and CRC cells is considered to be a contributing factor in promoting cancer progression (23). Adipocyte-derived medium can directly promote CRC progression, which also further suggests that CAAs are a positive factor in carcinogenesis (24). CAAs serve a vital role in promoting inflammation and angiogenesis. By comparing inflammation and angiogenesis in lean and obese patients with or without CRC, it was determined that the plasma levels of proinflammatory and angiogenic factors were at least partially elevated in obese patients with CRC. This study therefore revealed that peritumoral visceral AT is crucial for the development of CRC (25). Furthermore, to avoid the influence of individual differences on the experiment, *in vitro* experiments were conducted to compare the inflammatory reactions adjacent to and distant from the tumor site in the same patient. It was
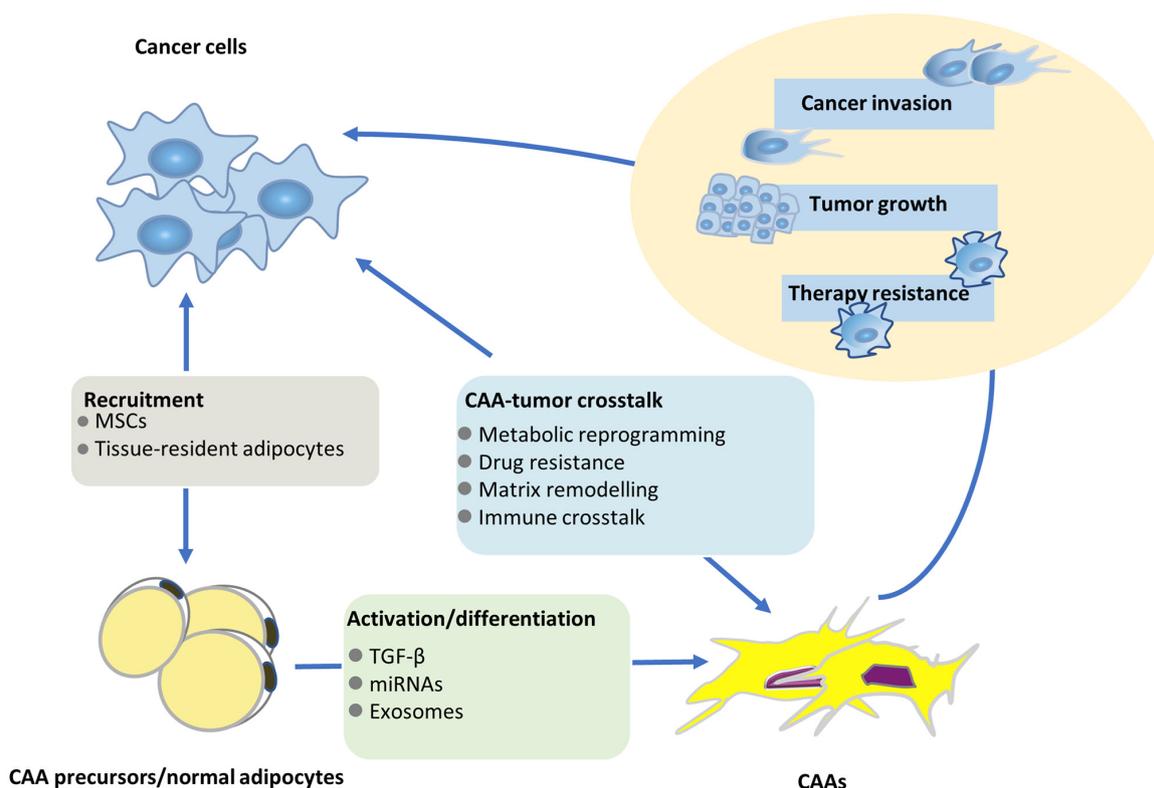
Figure 1. Complex relationships among tumors, adipocytes and CAAs. At the cancer invasion front, adipocytes undergo lipolysis and transform into CAAs. CAAs are involved in the progression and metastasis of tumor cells. CAAs can secrete a variety of adipokines, release free fatty acids and exosomes to cancer cells for metabolic reprogramming. Alternatively, after receiving signals from malignant cells, CAAs can produce various growth factors, adipokines and adipocytokines, which directly affect the growth and invasion of tumor cells. CAA, cancer-associated adipocyte; MSC, mesenchymal stem cell; miRNA, microRNA.

confirmed that the difference was due to the special influence of the tumor environment rather than due to the differences between individuals. However, this experimental result has not been confirmed *in vivo* (26). Another study demonstrated that the average levels of proinflammatory cytokines IL-6, IL-4 and granulocyte-macrophage colony stimulating factor in patients with obesity and CRC, were significantly higher than those in lean patients with CRC and patients with obesity only. The levels of other pro-inflammatory markers in the plasma displayed different trends; for example, IL-8 was only upregulated in patients with CRC and not obesity, whereas interferon γ and TNFα were upregulated in patients with obesity and not CRC. Plasma levels of numerous proinflammatory cytokines, including IL-1α, IL-6, TNFα, CCL-2 and plasminogen activator inhibitor-1 were increased in both patients with obesity and patients with CRC; however, there was no significant difference between obese and lean patients. Plasma VEGF levels were also upregulated in response to both CRC and obesity, which is consistent with results reported in a previous study (27). It has also been reported that the expression of inducible nitric oxide synthase (iNOS) increases under inflammatory conditions, such as pancreatitis or obesity (28). Under inflammatory conditions, nitric oxide (NO) is produced by iNOS, an enzyme primarily expressed by macrophages and to a lesser extent by adipocytes. In previous studies, the concentrations of nitrite and nitrate in medium were used as indicators to evaluate the release of NO under inflammatory conditions (27,28). Consequently, the inflammatory

characteristics of adipocytes away from and around the tumor site in both lean patients and patients with obesity and CRC were compared. The release of nitrite and nitrate in adipocytes around the tumor site was increased in lean patients with CRC compared with that in patients with obesity. However, adipocytes far from the tumor site did not show increased nitrite and nitrate secretions (29).

Previous studies have demonstrated that the TME has pro-inflammatory properties, which may contribute to the occurrence and progression of tumors (30). It can therefore be hypothesized that these pro-inflammatory factors in the TME may not only be due to increased macrophage infiltration as previously reported (31), but may also be derived from tumor-associated adipocytes. It has also been reported that the expression levels of cyclooxygenase-2 (COX-2) and peroxisome proliferator-activated receptor (PPAR)-γ are increased in the cancerous tissues of patients with CRC. Similarly, the gene expression of COX-2 and PPAR-γ is increased in tumor-associated adipocytes. A previous study has reported that the expression levels of COX-2 and PPAR-γ increase in the peritumoral tissues of patients with CRC. The gene expression levels of COX-2 and PPAR-γ are also increased in tumor-associated adipocytes (32).

Overall, the aforementioned studies indicate that the plasma levels of different pro-inflammatory and angiogenic factors in patients with CRC are increased, some of which may come from tumor-associated adipocytes. Tumor-associated adipocytes are considered a vital source of pro-inflammatory and angiogenic

factors, which may affect the progress of tumor biology and the clinical prognosis of the patients. A recent study has reported that an imbalance of intestinal microbiota caused by obesity increases harmful microbiota and metabolites and decreases beneficial microbes (including *Akkermansia muciniphila*) and metabolites (short-chain fatty acids) (33). In bile acid metabolism, bile acids promote the progression of CRC, especially in obese patients. Bile acid-dependent inhibition of the farnesoid X receptor (FXR) can promote the occurrence of CRC, which provides a theoretical basis for FXR to become an antitumor target in CRC in the future (33). The potential mechanism of obesity-promoting CRC therefore needs to be explored further.

CAAs in BC. BC is one of the most common cancer types worldwide and is the second highest cause of cancer-related mortality in women (34). The TME is a heterogeneous ecosystem composed of infiltrating immune cells, mesenchymal support cells and a matrix that promotes tumor progression. Adipocytes are the main cellular component of the BC microenvironment. Recent evidence demonstrates that adipocytes promote tumor progression via the interaction and dynamic communication between tumor cells and adipocytes (35). AT serves a key role as an energy reservoir, in which endocrine cells can produce various bioactive substances (14). A recent study has determined that the characteristics of adipocyte-derived cytokines change during tumor progression, which has been confirmed in human BC samples (36). Furthermore, an increasing number of studies have confirmed that adipocytes adjacent to invasive cancer cells, namely CAAs, participate in BC progression (17,36). Moreover, inflammatory factors secreted by CAAs can influence the behavior of BC cells, changing the characteristics and phenotypes of BC cells to increase invasiveness (36). Therefore, it can be hypothesized that abnormal AT, especially that adjacent to BC, is a highly complex participant in the interaction between the tumor and microenvironment and is regulated by BC cells. This interaction may be amplified as a result of the malignant function of CAAs (16).

In the microenvironment of BC, the expression and secretion profiles of CAA-mediated inflammatory factors are altered. The secretion of CCL2, CCL5 (36), IL-1β, IL-6 (35), TNFα, VEGF and leptin (37) is increased in the BC microenvironment, further promoting the proliferation, invasion and angiogenesis of tumor cells. Therefore, CAAs promote the tumorigenesis, invasion and metastasis of BC. Furthermore, CAAs in the treatment of BC such as chemotherapy, radiotherapy, hormone therapy and immunotherapy can result in tumor resistance, leading to the persistence of residual tumors and an increased risk of tumor recurrence (16). Moreover, when mature adipocytes transform into CAAs, tumor cells become metabolic parasites by ingesting metabolites such as ketones, pyruvate, fatty acids and lactic acid from CAAs. Consequently, tumor cells transition from relying on anaerobic glycolysis to preferentially using fatty acids for fatty acid oxidation to provide energy for themselves (38-40). The regulatory mechanisms of CAAs in BC are complex, including adipokine secretion, metabolic reprogramming and extracellular matrix (ECM) remodeling. Several hypotheses have been proposed stating that obesity promotes the development and progression of BC (39,40). However, the underlying mechanisms remain unclear due to a lack of sufficient models to study the relationship between obesity and BC.

CAAs in ovarian cancer. The biological characteristics of ovarian cancer are different from those of other types of the cancer, as ovarian cancer can exhibit hematogenous metastasis, which is rare and often limited to the AT-rich omentum (41). Although experiments have confirmed that the adipocytes in the omentum are the key to inducing ovarian cancer cell omental metastasis, the specific mechanism remains unclear. According to recent studies, secretory acidic cysteine rich protein (SPARC) may serve a role in this process (42,43). SPARC is an ECM protein, which serves an important role in maintaining the homeostasis of the surrounding tissue environment. SPARC can serve a role in tissue remodeling, including in the regulation of adipocyte differentiation. SPARC can also inhibit adipocyte production, reduce the production of CAAs, interfere with the interaction between cancer cells and mesothelial cells, and normalize the TME (42). Previous studies have demonstrated that the protein and lipid metabolomics of ovarian cancer cells change significantly following coculture with adipocytes. Among them, fat chaperone protein FABP4 was induced in tumor cells by adipocytes, and makes the cancer cells more invasive and metastatic, which serves a key regulatory role in changes to lipid metabolism in cancer cells. Furthermore, targeting FABP4 can reduce the metastasis of cancer cells to the greater omentum and improves cell sensitivity to carboplatin (42-44). Another study demonstrated that the selective metastasis of ovarian cancer to the greater omentum is caused by the CCL2 receptor, C-C chemokine receptor type (CCR)2, on ovarian cancer cells (44). CCL-2 is produced by the binding of omental adipocytes to homologous receptor CCR2 on ovarian cancer cells, which promotes cancer cell migration and omental metastasis by activating related signaling pathways such as the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway. Metformin can specifically inhibit the secretion of CCL-2 and therefore serves a role in the treatment of ovarian cancer (44). To help understand the cause of omental metastasis in ovarian cancer, a previous study has verified that primary omental adipocytes can induce the proliferation and invasion of ovarian cancer cells both *in vivo* and *in vitro* (45). CD36 is a transmembrane glycoprotein belonging to the class B scavenger receptor family. CD36 promotes the uptake of fatty acids and cholesterol and transmits intracellular signals to regulate fatty acid metabolism in tumor cells. Furthermore, CD36 serves a crucial role in the bioenergy adaptation of OVCA cells in an adipocyte-rich microenvironment. Omental adipocytes can reprogram tumor metabolism by upregulating oocyte CD36 expression (46). Functional studies have demonstrated that miR-21 combined with apoptotic protease activating factor-1, a new direct therapeutic target, could inhibit the apoptosis of ovarian cancer cells and induce chemotherapy resistance (47). Furthermore, evidence suggests that the tumor-promoting effect of CAAs results from both systemic and local effects of hormones involved in lipid hemostasis mediated by direct contact, paracrine factors or both (47). In the microenvironment, CAA will affect the transformation of the metabolic phenotype of ovarian cancer, which plays an important role in the occurrence and development of ovarian cancer (48).

4. Mechanistic insights linking CAAs with cancer

Although there is increasing evidence to suggest that CAAs are positively correlated with certain types of cancer, the underlying molecular mechanisms remain unclear. CAA induces abnormal metabolic reprogramming (among which lipids serve an unusual role in the process of tumor progression, as well as being a metabolic substrate), chemoresistance and the secretion of various adipokines, which may serve important roles in the complex process of carcinogenesis.

Metabolic reprogramming. Metabolic reprogramming to meet the bioenergetic and biosynthetic demands, and maintain redox balance and cell proliferation, is a hallmark of cancer (49). From benign growth to malignant and invasive lesions, the changes of cell metabolic requirements are complex and dynamic. With uncontrolled proliferation, cancer cells need increasing amounts of biomolecules to produce new sister cells. The metabolic substrates of these cancer cells change when they invade the surrounding stromal tissue and interact with new cell types. Furthermore, when tumors metastasize, cancer cells face a series of new metabolic challenges in different environments. Therefore, cancer cells need to adjust their metabolic programs to adapt to a constantly changing situation.

Adipocytes adapt to their own metabolic processes through dynamic interactions with tumors, which further supports the proliferation of tumor cells (50). Furthermore, to meet the extreme energy requirements of cancer cells, CAA metabolic reprogramming that occurs involves alterations in the metabolism of macronutrients, including carbohydrates, lipids and amino acids (51). In terms of glycolysis, the tricarboxylic acid cycle, amino acids, nucleotides and lipid metabolism, the metabolic processes in cancerous and healthy tissues are substantially different (39). As described by the 'Warburg effect', cancer cells prefer to produce adenosine triphosphate by glycolysis despite the presence of oxygen (52,53). However, in order to adapt to the environmental changes of hypoxia and acidosis, the metabolic pattern of cancer cells changes to rely on lipid metabolism, especially fatty acid oxidation (54). Furthermore, cancer exhibits heterogeneity in genetic and microenvironmental parameters that influence cell metabolism. For instance, tumor metabolism influences, and is influenced by, the metabolite composition of the TME, while the interorgan and intratumor microenvironments define the metabolic properties of tumor cells. The TME serves an irreplaceable role in tumor metabolism. The 'reverse Warburg effect' describes how glycolytic metabolism in the cancer-related matrix supports adjacent cancer cells. The catabolic products include lactate monocarboxylate, pyruvate and ketone body. The transfer of these catabolic products can induce metabolic coupling of interstitial carcinoma, inducing cancer cells to produce ATP, increase their proliferation and reduce cell death. The 'reverse Warburg effect' is also important when cancer cells utilize the energy generated from stromal cells in the TME (2). As one of the main components of the TME, tumor cells inevitably use free fatty acids and glycerol produced by fat cell catabolism as energy sources (55,56). Tumor lipid metabolism is regulated by genetic and epigenetic changes in the tumor cells, which affects the process of receiving lipid from CAAs as a metabolic substrate. Fatty acids can be released from lipid droplets via the adipose triglyceride lipase (ATGL)-dependent lipolysis pathway. ATGL expression in cancer cells is upregulated by the interaction between adipocytes and cancer cells (38). Through the co-culture of adipocytes and cancer cells, it has been determined that free fatty acids in adipocytes can be transferred to cancer cells. This process can upregulate CPT1A and other various protease expression levels acting on the electron transfer chain, which promotes fatty acid metabolism in cancer cells (57). Tumor cells can not only increase the expression of ATGL to accelerate the utilization of adipocyte-derived lipids, but also enhance the intracellular transport of fatty acids by increasing the expression of FABP5 (58). CD36 and fatty acid transporter-1 (FATP1) are mainly expressed in cancer cells adjacent to AT (5). Zaoui *et al* (59) reported that cancer cells could regulate their metabolic reprogramming via exogenous fatty acid uptake mediated by CD36 on the cell surface. Moreover, adipocyte-induced expression of CD36 and FATP1 promotes tumor progression by facilitating signal transduction in tumor cells (60-62). Wang *et al* (63) reported the role of Janus kinase (JAK) and signal transducer and activator of transcription 3 (STAT3) signaling pathways in regulating lipid metabolism. Inhibition of the JAK/STAT3 signaling pathway inhibits the expression of numerous lipid metabolism genes, including CPT1B, which encodes a key enzyme of fatty acid oxidation (FAO). Adipocytes also affect immune cell metabolism. Adipocyte-derived leptin can change the metabolic pattern of CD8+ T cells via activation of STAT3-FAO and inhibiting glycolysis, leading to the downregulation of the effector function of CD8+ T cells (64).

CAA-derived lipid metabolism. Although previous studies have shown that lipids are mainly involved in the metabolic dynamics of the interaction between tumor cells and stromal cells, lipids can also play an additional role in the TME as a material source of cell membrane synthesis and an energy source of cancer cells (45,65,66). Certain tumor-associated stromal cells have been demonstrated to secrete autotoxin (ATX) (67). ATX hydrolyzes lysophosphatidylcholine to lysophosphatidic acid (LPA). LPA can be used as a signaling molecule in cancer cell mitosis and migration (68). Furthermore, adipose-derived stem cells and adipocytes in the TME can also produce ATX. Once cancer cells begin to invade surrounding tissues, inhibition of ATX has no significant effect on the growth of the primary tumor. However, disruption of the LPA/ATX axis helps to reduce cancer cell metastasis (69-71). Moreover, studies on metabolic determinants supporting the metastatic potential of cancer cells have determined that lipid metabolism is a major promoter (72). It is now widely recognized that cancer cells with high metastatic potential often express CD36 and that mice fed with a high-fat diet exhibit an increase in the size and quantity of tumor lymph node metastases in a CD36-dependent manner (73). Moreover, numerous types of cancer, including melanoma, BC and prostate cancer, first pass through lymphatic vessels to the proximal lymph nodes, where lipid metabolism can be used as a driver for lymphangiogenesis (72,73). Furthermore, a previous study on the role of neutrophils in supporting lung colonization by metastatic BC cells, revealed that the destruction of leukotriene producing

enzyme arachidonic acid 5-lipoxygenase, could significantly inhibit the pre-metastasis activity of neutrophils. These results suggested that lipid metabolism is not only involved in the initiation of cancer cell metastasis, but also in the colonization of peripheral metastasis sites (74).

ECM. In the TME, the ECM is composed of non-cellular polymer proteins and helper molecules. The ECM is an important component in the TME that determines cancer progression (75). Metastasis is the main cause of cancer-related mortality, but the metastasis of cancer cells into a new environment requires a cellular adaptation process. Cancer cells can achieve their own TME homeostasis via an interaction with the ECM. This functional adaptability needed in order to survive in a changing environment is called cancer cell phenotypic plasticity (76). ECM remodeling consists of two stages (the transformation from epithelial cells to mesenchymal cells, and the transformation from mesenchymal cells to epithelial cells) among which the transformation from epithelial to mesenchymal cells is established; however, there are few studies on this transformation process (77). The reason cancer cells can multiply indefinitely without being regulated by the body is that they can dedifferentiate and acquire stem cell-like characteristics. When the surrounding environment is relatively stable, cancer cells are also in a dormant state. However, in the case of external abnormalities, cancer cells can initiate TME remodeling and epithelial-mesenchymal transition (EMT), obtaining a stronger motor ability (77,78). The erosion and metastasis of malignant tumor is a dynamic and continuous process. Tumor cells first migrate from the primary site, invade the ECM, adhere to some molecules in the basement membrane and intercellular matrix, activate cells to synthesize and secrete various degrading enzymes, as well as assist tumor cells to enter blood vessels via the ECM. Then, tumor cells operate under the action of some factors, penetrate the blood vessel wall to the secondary site where they continue to proliferate and undergo metastasis. In short, abscission, adhesion, degradation, movement and proliferation occur through the whole process of malignant tumor erosion and metastasis. Therefore, it is not difficult to observed that the tumor will obtain a stronger metastatic ability when the tumor cells undergo the EMT process (77,78). However, a previous study has demonstrated that EMT is related to epithelial cell integration at the distal metastatic site of cancer cells (78). The reason why ECM has such a great impact on the TME remodeling of cancer cells remains to be fully elucidated.

Previous studies have, however, demonstrated that CAAs affect tumor ECM remodeling (75,79). CAA-induced TGF-β expression can inhibit AT angiogenesis. Inhibition of angiogenesis can lead to hypoxia and fibrosis in AT, thereby mediating the occurrence of the EMT in BC cells (79). Adipocytes extracted from AT around prostate tumors were found to highly express proteins that regulate ECM structure, including TNFα, osteopontin and MMP9 (80). CAAs can also promote the invasiveness of renal cell carcinoma cells via leptin (81). Furthermore, adipocytes secrete and process type VI collagen, which provides survival promoting signals in the early stages of breast tumor growth. The type VI collagen cleavage product, endothelin, also serves an important role in the subsequent occurrence and development of BC (82).

Overall, these observations suggest that CAAs may act as proto-cancerous stromal cells to remodel the ECM and create a tumor tolerant environment.

Drug resistance. CAAs in the TME serve a dynamic and complex role in the drug response and promotion of tumor growth (83). Both adipocyte and tumor lipid metabolism can affect the tumor drug response. CAAs provide metabolic substrates, growth factors and cytokines to tumor cells. CAAs can transdifferentiate into other stromal cells to change the growth environment and adjust the drug response of the tumor. In a variety of solid and non-solid types of cancer, adipocyte and lipid metabolism-mediated chemotherapy resistance involves a host of complex mechanisms (83,84). To date, there are two types of drugs used for targeted cancer therapy: i) Drugs targeting cancer cells; and ii) drugs targeting cellular and molecular components in the TME. Among the drugs targeting the cellular and molecular components of the TME, targeting tumor vessels with anti-angiogenic drugs (AADs) has become key to the treatment of numerous types of cancer (84). These drugs are usually combined with conventional chemotherapy drugs (85). In the present review, mainly the role of CAAs and lipid metabolism in anti-vascular drug resistance is discussed. Epidemiological evidence suggests that patients with obesity have poorer clinical outcomes than non-obese patients who receive the same treatment (86,87). However, in general, obese patients with cancer are in the advanced stages at the point of diagnosis (85-87). The drug resistance properties of advanced cancer are therefore the main reasons why it is difficult to treat.

Previous studies have demonstrated that BC, ovarian cancer and prostate cancer rich in AT grow faster and more aggressively than those with less AT (88,89). Research into the reasons for this phenomenon has revealed a number of results. Adipocyte volume is increased in patients with obesity, resulting in an increased distance between capillaries. Owing to the relatively low density of microvessels the blood perfusion in the AT of patients with obesity is insufficient (90). Therefore, in patients with obesity, AT undergoes mild hypoxia, which affects the cellular and molecular composition of the adipose microenvironment. These changes inevitably affect the drug response of tumors growing in the vicinity of obese AT and may limit the distribution of anticancer drugs. Although tumor tissue is rich in blood vessels, the growth of tumors in anoxic obese AT may be due to decreased blood vessels and poor perfusion of disordered, tortuous and leaky vessels in the tumor itself, which results in restricted drug perfusion (91). A previous study has determined that tumors implanted with the same gene at different sites exhibit different responses to AAD treatment, which provides evidence that the tissue environment outside the tumor serves an important role in AAD resistance (92). Implantation of pancreatic ductal adenocarcinoma and CRC tumors in AT results in intrinsic AAD resistance, whereas the same tumors growing in non-AT are sensitive to the same AAD treatment (92). Similarly, AAD-sensitive hepatocellular carcinoma (HCC) growing in steatotic livers is resistant to anti-angiogenic therapy, whereas HCC in non-steatotic livers remains sensitive. These preclinical findings are thought to be associated with AAD resistance and the AT environment (84,92). Unexpectedly, for the stromal component of
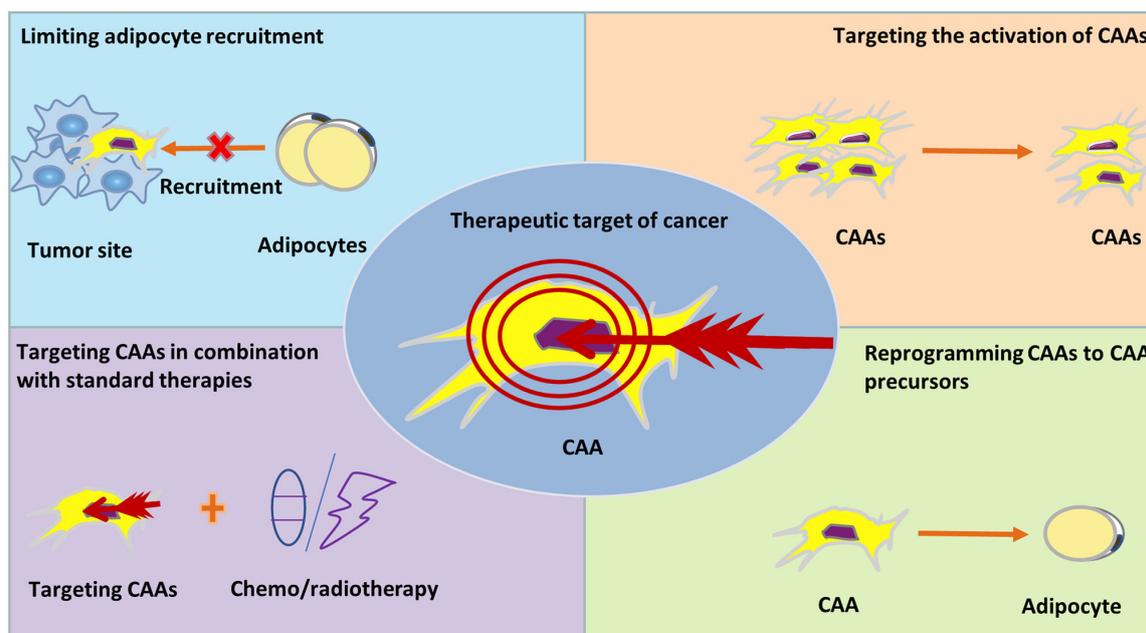
Figure 2. Potential methods for targeting CAAs in the treatment of tumors. Potential therapeutic approaches include limiting adipocyte recruitment, targeting the activation of CAAS, reprogramming CAAs to CAA precursors and targeting CAAs in combination with standard therapies. CAA, cancer-associated adipocyte.

tumors, the microvessels of almost fat-free tumors and fat-rich tumors are equally sensitive to AAD treatment (92). Tumor growth depends on active angiogenesis, and the inhibition of angiogenesis weakens tumor growth. However, tumors in the adipose environment can continue to grow into large masses, even with a small amount of intratumoral microvascular tissue. Furthermore, angiogenesis has been shown to inhibit tumor growth in non-ATs (93). Thus, the unexpected discovery of tumors growing in AT distinguishes anti-angiogenic responses from tumor growth. Adipose vessels seem to be dependent on VEGFs. For anti-VEGF targeted treatment, inhibiting VEGF leads to significant vascular degeneration (94,95). Therefore, tumors growing in AT experience more severe hypoxia than those growing in non-AT. AAD-induced vascular reduction and hypoxia can limit the supply of circulating glucose, resulting in an impaired glucose-dependent metabolism (96). To survive and proliferate, cancer cells must use alternative energy mechanisms to generate energy. AAD-triggered hypoxia results in the following three lipid metabolic processes: i) The release of free fatty acids and glycerol as metabolites from adipocytes; ii) cancer cells increase free fatty acid uptake by upregulating CD36; and iii) cancer cells undergo metabolic pathway reprogramming, which activates the β-oxidation pathway resulting in free fatty acid metabolism-dependent energy production, supporting tumor growth and metastasis (17,97). These processes are illustrated in Fig. 2. Based on these findings, targeting CAAs and lipid metabolism will provide an attractive approach for cancer therapy. Compared with the use of a single drug, the combination of AAD and β-oxidation inhibitors (for example, etomoxir, a CPT1 inhibitor) has greater anticancer effects in animal models of HCC grown in steatotic livers (92). Furthermore, clinical studies have demonstrated that obesity is negatively associated with clinical benefits, such as decreased sensitivity of chemotherapeutic drugs and poor prognosis, in

patients treated with anti-angiogenic therapies (98). Hypoxia induced by anti-VEGF treatment results in the high expression of IL-6 and fibroblast growth factor 2 (FGF2) (99). Similarly, anti-VEGF treatment can induce high expression levels of IL-6 and FGF2 in patients with BC, which contribute to AAD resistance (98,99). Furthermore, the number of adipocytes in tumors was directly and positively correlated with adverse AAD reactions (100).

5. Adipokines

Adipocytes can secrete >600 metabolites, hormones and cytokines, collectively known as adipokines (5). Although large-scale Mendelian randomization analyses have been performed to assess the possible causal relationship between adipokine concentrations and the risk of obesity-related cancer, including CRC and ovarian cancer, the results have demonstrated that there is no causal relationship (101). Adipokines serve an active role in regulating a variety of biological mechanisms, including insulin secretion, fat distribution, inflammatory response and energy consumption (5). The crosstalk between adipocytes and BC cells favors tumor proliferation, survival and metastasis (102). In terms of adipokines, CAA secretes more chemokines, such as CCL2, CCL5, IL-1β, IL-6, TNFα, VEGF and leptin, compared with relatively normal adipocytes (37), which can promote tumor invasion and metastasis (40,103). CAAs can also promote tumor growth and metastasis, compared with distant mature adipocytes, through fewer physical barriers (such as thickness and distance) and more active adipokine secretions (5). Furthermore, in addition to the aforementioned adipokines, the interaction between CAAs and cancer cells involves a variety of specialized adipokines, including resistin, insulin-like growth factor (IGF)-1, hepatocyte growth factor,

Table I. Examples of cancer associated adipocyte-derived adipocytokines.

Factor	Receptor	Pathways/key genes	Function	(Refs.)
Leptin	OBR	ER signal, JAK/STAT3, PI3K/AKT, IL-1/IL-1R, VEGF/VEGFR, FAK and SRC-1/STAT3	Proliferation, differentiation, metastasis, self-renewal and chemoresistance and angiogenesis	(52,90,93-98)
Adiponectin	AdipoR1/AdipoR2	ERK1/2, AKT, TNFα, IL-1β, NF-κB, IL-6, IL-8, STK11 and AMPK/ULK1, AMPK and PI3K/AKT	Negatively regulating cancer cell growth, autophagy, inhibiting proliferation and invasion	(5,101)
CCL2	CCR2/4	Notch1, CXCL12 and CLS	Inducing the activity of CSCs, inflammation and malignant progression	(111-114)
CCL5	CCR5	ERK, EMT, AKT/mTOR	Inflammation, poor DFS and OS	(119,120,123)
IL-6	IL-6R/gp130	NF-κB, STAT3, EMT	Migration, proliferation, invasion and pro-inflammatory response	(134,135,138)

CCL, chemokine (C-C motif) ligand; CCR, C-C chemokine receptor type; OBR, leptin receptor; AdipoR, adiponectin receptor; IL-6R, IL-6 receptor; gp130, glycoprotein 130; ER, estrogen receptor; JAK, Janus kinase; IL-1R, IL-1 receptor; FAK, focal adhesion kinase; SRC-1, steroid receptor coactivator-1; STK11, serine/threonine kinase 11; AMPK, adenosine 5'-monophosphate-activated protein kinase; ULK1, Unc-51 like autophagy activating kinase; CXCL12, chemokine (C-x-C motif) ligand 12; CLS, crown-like structure; CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; DFS, disease-free survival; OS, overall survival.

platelet-derived growth factor BB, IL-1, IGF binding protein-2 and granulocyte colony stimulating factor (104-106). In the subsequent sections of the present review, focus is given to the emerging roles of CAA-derived leptin, adiponectin, IL-6, CCL2 and CCL5 adipokines in cancer. Understanding the mechanisms of CAA-derived adipokines is important for understanding the behavior of tumor cells and formulating new therapeutics (Table I).

Leptin. Leptin is a hormone with a molecular weight of 16 kDa, encoded by the LEP gene on human chromosome 7, and is mainly synthesized and secreted by adipocytes (107). Leptin is also produced by cancer cells (108). Leptin mediates multiple biological functions, including proliferation, differentiation, inflammation and nutrient absorption via the leptin receptor (OBR) (107), serving a role in the development and proliferation of normal and malignant tissues. It has been reported that increased leptin serum levels are positively correlated with cancer risk and with increased plasma leptin levels in patients with cancer. High leptin levels are also correlated with a high cancer grade, advanced tumor stage and invasive cancer subtypes, such as in BC and CRC (107). Compared with distant tumor sites, the expression of leptin in AT at the infiltration front is higher (109). Furthermore, the production and secretion of leptin is higher in CAAs than that in mature adipocytes (107). Therefore, leptin is involved in the interaction between adipocytes and cancer cells (16). Leptin may regulate numerous aspects of the occurrence, development and metastasis of BC via autocrine, endocrine and paracrine signaling pathways (5,16). Leptin can activate the estrogen receptor, JAK/STAT3 and PI3K/AKT signaling pathways to promote the proliferation of BC cells (91). Leptin accelerates the cell cycle of BC cells by increasing the expression of cyclinD1 and cyclin-dependent kinase 2 (110). Moreover,

leptin can upregulate the mRNA and protein expression levels of IL-1/IL-1 receptor (IL-1R), further promoting the expression of VEGF and VEGFR, which promote angiogenesis (111). The role of leptin in BC invasion and metastasis has been thoroughly researched. Wei *et al* (112) reported that leptin promoted the EMT of BC cells via two main mechanisms: i) By upregulating the expression of pyruvate kinase M2; and ii) by activating the PI3K/AKT signaling pathway (112). Leptin also activates focal adhesion kinase to enhance the secretion of ECM remodelers via the steroid receptor coactivator-1/STAT3 signaling pathway, which suggests that leptin is associated with the establishment of a more invasive phenotype in BC cells (113). Previous studies have demonstrated that tumor cell proliferation and tumor growth are significantly reduced in leptin-deficient tumors; however, leptin-deficient and leptin receptor-deficient mice are severely obese. Moreover, OBR expression levels are significantly increased in colon tumors compared with those in the normal epithelium. Colonic leptin signaling-mediated CRC growth mainly occurs via the OBR/STAT3 signaling pathway (114). A previous study has demonstrated that adipocyte-derived leptin and IL-6 promote the local invasion and metastasis of tumor cells, which occurs by activating procollagen-lysine and 2-oxoglutarate 5-dioxygenase (lysine hydroxylase) 2 when tumor cells are co-cultured with mature adipocytes. Furthermore, leptin may promote BC invasion and metastasis via the PI3K/AKT/activating transcription factor-2 signaling pathway in tumor cells (115,116). Leptin also regulates the function of immune cells. Leptin can promote the progression of BC by activating STAT3-FAO, inhibiting glycolysis and downregulating the effector function of CD8+ T cells (64).

Adiponectin. Adiponectin, a hormone with a molecular weight of ~30 kDa, is encoded by the ADIPOQ gene (117,118).

Adiponectin serves a protective role in tumor progression by binding to adiponectin receptor 1 and adiponectin receptor 2. The decrease in adiponectin secretion in CAAs (108) suggests a relationship between adiponectin and its related signaling proteins in antitumor activity. Adiponectin negatively regulates the cancer cell proliferation by regulating inflammatory signaling molecules, such as extracellular signal-regulated kinase (ERK)1/2, AKT, TNFα, IL-1β, nuclear factor (NF)-κB, IL-6, IL-8 and CCL2 (118). Autophagy is a fundamental vacuolar lysosomal degradation process known to help prevent the accumulation of damaged proteins and organelles, recycle cytoplasmic components and maintain intracellular homeostasis (119). Adiponectin secreted by adipocytes is an effective inducer of cytotoxic autophagy. CAAs are functionally diverse and can induce adipocyte senescence via the adiponectin-dependent autophagy signaling pathway, thereby enhancing malignant behavior (120). Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) is an important energy sensor that can be regulated by cytokines, such as leptin and adiponectin, promoting autophagy, regulating cellular metabolism and maintaining energy balance (121). Chung et al (119) proposed that adiponectin can induce cancer autophagy and is involved in the regulation of the serine/threonine kinase 11 and AMPK/Unc-51 like autophagy activating kinase (ULK1) axes. ULK1 is an autophagy-initiating kinase. Under nutrient sufficient conditions, mTOR disrupts the interaction between ULK1 and AMPK by inhibiting the activation of ULK1 (122). Moreover, adiponectin can inhibit the growth and invasion of BC cells and induce apoptosis by triggering the AMPK signaling pathway and inhibiting the PI3K/AKT signaling pathway (107). In patients with obesity, this relationship uses the adiponectin to leptin ratio, compared with patients who are not obese, and poses a significant problem. Theriau et al (123) revealed that a low ratio of adiponectin to leptin in patients with obesity can rapidly induce MCF-7 BC cells to enter the cell cycle (123). Therefore, this increase in adiponectin levels and the decrease in the leptin-to-adiponectin ratio are related to a decrease in BC growth. In CRC, AT in the TME leads to systemic low-grade and subclinical inflammation, which is conducive to the carcinogenesis of various tissues in the body. However, AT with endocrine activity influences the risk of systemic carcinogenesis directly related to inflammation and by significantly reducing the expression of adipokines, especially adiponectin (124). Adiponectin and its receptors, can induce the activation of various mechanisms, thus exerting a cancer-preventive effect. Adiponectin participates in the AMPK signaling pathway to regulate the cell cycle by regulating the activity of various transcription factors, including p53, and has been reported to inhibit signaling pathways involved in proliferation, such as the Mtor (125), Wnt/GSK3β (126) and JAK/STAT signaling pathways (127). Furthermore, a previous study reported that adiponectin can inhibit cell proliferation (128). The low mRNA expression levels of COX-2 and high expression levels of T-cadherin in CRC HCT116 cells suggest that adiponectin may directly inhibit tumor growth via COX-2 (129).

CCL2. The chemokine CCL2 is encoded by the CCL2 gene and is also referred to as MCP-1 (130). In the TME, different cells, including cancer cells, endothelial cells and fibroblasts, can secrete CCL2 into the extracellular environment. CCL2 binds to G protein-coupled receptors CCR2 and CCR4, and acts as a chemoattractant to recruit CCR2-expressing immune cells to inflammatory regions (130). A previous study found that CCL2 expression levels increased in BC e0771 cells, which recruited more adipocytes and monocytes/macrophages (39). High expression levels of CCL2 are associated with decreased survival in patients with BC (131). Tsuyada et al (132) reported that BC cells secrete cytokines by activating the STAT3 promoter and consequently the STAT3 signaling pathway in fibroblasts, resulting in increased CCL2 expression and secretion. CCL2 can also induce Notch1 expression and downstream signaling pathways in BC cells, thereby inducing cancer stem cell (CSC) activity. Furthermore, CCL2 expression is significantly correlated with angiogenesis (133). CCL2 may also serve an important role in the crosstalk between adipocytes and macrophages. Studies have found that increased expression levels of CCL2 and IL-1β in AT induce macrophages to secrete chemokine (C-x-C motif) ligand 12 (CXCL12), which is associated with obesity (134,135). It has also been demonstrated that mammary epithelial cells surrounding AT recruit macrophages and form a crown-like structure by secreting CCL2, which is related to the malignant progression of BC. CCL2 has been proposed as a therapeutic target for metastatic BC (134-136). In the presence of BC cells, adipocytes can revert to an immature proliferation phenotype, increasing the production of adipocyte-derived CCL2 and promoting cell migration through adipokines such as IL-6 and CCL2 (15,136). Furthermore, neutralization experiments using anti-IL-6 or CCL2 antibodies have demonstrated that the migration enhancing effect of CAA-conditioned media can be abolished (15). A recent study has determined that chronic inflammation induced by CCL2 can significantly promote tumor growth and connective tissue matrix formation via the early entry of macrophages and fibroblasts into the TME (137).

CCL5. Chemokine CCL5 has a molecular weight of 8 kDa and is located on chromosome 17q12; it is an effective chemokine that attracts leukocytes and is a multifunctional inflammatory mediator that can be expressed by BC cells (138). CCL5 is highly expressed in BC and can also be produced by a variety of cells, including mesenchymal stem cells (139). CCL5 overexpression is associated with ERK phosphorylation in tumor cells and with low 5-year disease-free survival and overall cancer survival in patients with early human epidermal growth factor receptor-2 (HER2)-positive BC (140). The abundance of CCL5 in the peritumoral AT of patients with triple negative BC (TNBC) is also associated with parallel low tumor metastasis and overall survival. Song et al (141) demonstrated that when adipocytes were cocultured with a TNBC cell line, adipocytes could enhance the EMT effect by secreting more CCL5. Karnoub et al (103) reported that BC cells stimulate the secretion of CCL5 and that paracrine CCL5 reversibly binds to CCR5 on the membrane surface of human BC MDA-MB-231 cells to enhance migration, invasion and metastasis (103). Another study demonstrated that when MDA-MB-231 TNBC cells were co-cultured with human adipocytes, CCL5 levels were increased in the surrounding tissues, resulting in the enhancement of MDA-MB-231 cell invasion and metastasis ability (36). Therefore, antagonizing CCL5 using specific

CCL5 small molecule inhibitors can reduce the invasion of BC cells (36). Numerous studies have demonstrated that the CCL5/CCR5 axis is highly activated in TNBC and HER2-positive BC. The invasive ability of CCR5$^+$ BC cells that responded to CCL5 was 40x higher compared with that of CCR5$^-$ cells that did not respond to CCR5 (142-144). In the mTOR-dependent mechanism, MCF-7 cells overexpressing CCR5 have a stronger proliferation ability (145). Moreover, it has been shown that inhibition of CCL5/CCR5 signaling in endothelial cells leads to the defective activation of the AKT/mTOR signaling pathway and abnormal vascular and tumor growth *in vitro* and *in vivo* (36). Therefore, stromal cells may secrete CCL5 into the TME, where CCL5 may activate the AKT/mTOR signaling pathway to promote tumor metastasis by binding to CCR5. Moreover, CCL5 partially impairs triglyceride synthesis in adipocytes via its cognate receptors by downregulating the production of lipase and sterol regulatory element binding protein-1 (146). CCL5 also recruits macrophages (147) and T helper 1 and T helper 17 cells (148) in the TME, which can induce and maintain the striated structure of the matrix in the inflammatory microenvironment. This structure allows carcinogenic cell behavior and is destroyed by blocking CCL5 *in vitro* during matrix deposition (149). Therefore, CCL5 could be a potential target for BC precision therapy, but its specific mechanism requires further investigation.

IL-6. The level of IL-6 secreted by adipocytes is significantly increased under the pathological conditions of obesity and cancer. IL-6 is a cytokine involved in multiple biological activities, including hematopoiesis, immune regulation and tumorigenesis (150). Following coculture with BC cells, the expression and secretion of IL-6 in adipocytes increases (151). Among the proinflammatory cytokines involved in obesity-related inflammation, IL-6 has been determined to be the most important in CRC pathogenesis (15). IL-6 serves an important role in CRC, which may be related to the expression of the IL-1β/IL-6 network in the TME. The significance of this finding stems from the regulation of IL-6 synthesis by IL-1β and its synergistic pro-inflammatory effects. Lee *et al* (152) demonstrated that mouse 3T3-L1 adipocytes indirectly cocultured with BC cells upregulated the expression of IL-6 and pentraxin 3, which is consistent with the overexpression of IL-6 observed in CAAs of human BC tissue (152). Furthermore, IL-6 acts as an independent poor prognostic factor for overall survival and is associated with poor 5-year disease-free survival in patients with steroid-refractory metastatic BC (153). IL-6 promotes tumor cell proliferation, survival and angiogenesis by regulating the JAK/STAT3 signaling pathway (154). In HER2-positive BC, IL-6 can also induce the generation and maintenance of BC CSCs via the NF-κB and STAT3 signaling pathways to promote tumor progression (155). IL-6 also regulates the self-renewal of BC CSCs and promotes the survival and proliferation of stem cells when the Notch, Wnt and TGF-β signaling pathways are activated (156). Nickel *et al* (157) demonstrated that the migration ability of TNBC cells was significantly increased and the secretion of IL-6 was increased following coculture with adipocytes (157). Moreover, adipocyte-derived IL-6 can also enhance the invasive behavior of BC cells and induce the EMT phenotype (158). IL-6-induced BC metastasis is reversed

when the IL-6 receptor (IL-6R) is blocked by an anti-IL-6R antibody (159,160). Blocking IL-6 signaling in BC cells alters the expression of EMT regulatory genes, disrupts the stability of focal adhesions and decreases the mobility of cells (161).

6. Conclusions

CAAs significantly affect tumor growth, metastasis and drug sensitivity via multiple mechanisms, including para-crine, juxtacrine and endocrine signaling, metabolites and metabolic reprogramming. This effect is greatest in tumors that are closely related to adipocytes, such as BC, CRC and ovarian cancer. Therefore, targeting CAAs and lipid metabolism would be a potential approach for cancer treatment. Furthermore, adipocytes are excellent candidates for altering tumor behavior via heterotypic signal transduction processes that secrete adipokines, such as hormones, growth factors, cytokines and other molecules. In the TME, the expression and secretion profiles of inflammatory mediators in adipocytes are altered. The secretion of chemokines, such as CCL5, CCL2, IL-6 and leptin, further promotes the proliferation, invasion and angiogenesis of tumor cells.

In summary, the present review mainly focused on the role of CAAs in cancer. The link between CAAs and cancer is important, and great progress has been made to elucidate the underlying biological mechanisms of CAA and the pathogenesis of cancer. CAAs induce leptin, IL-6, TNFα, CCL2 and CCL5 expression and disturb gut microbiota and bile acid homeostasis. These changes promote carcinogenesis, mediated by downstream signaling pathways. Based on the current understanding of this mechanism, several promising methods can be proposed for CAA in the treatment of tumors. However, several challenges remain for CAA identification. Certain CAA-related genes and protein markers have been identified, but there are no uniform criteria for the authentication of CAAs. An increased understanding of the link between CAA risk factors and carcinogenic processes will help develop more promising therapeutic targets and approaches for CAA-related cancer treatment in the future.

Availability of data and materials

Not applicable.

Authors' contributions

The concept, design and drafting of the review were performed by HY and SH. Data collection, involving searching, analyzing and summarizing the literature, was carried out by HY and

manuscript revision was performed by SH. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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