

Adipocytes as Orchestrators of Multimodal Cancer Therapy Resistance

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Abstract

The emergence of therapy resistance remains a formidable barrier to successful clinical outcomes in oncology, necessitating a deeper understanding of the tumor microenvironment (TME) as a dynamic ecosystem. Adipocytes, once viewed as passive energy reservoirs, are now recognized as active orchestrators of tumor progression and multimodal therapy resistance, particularly in adipose-rich malignancies. This review comprehensively delineates the multifaceted mechanisms through which adipocytes shield cancer cells from therapeutic insults, including chemotherapy, targeted agents, and immunotherapies. We analyze the clinical evidence positioning visceral adiposity as a critical determinant of treatment failure and explore the complex molecular interplay driven by the adipocyte-derived secretome, lipid metabolite-mediated metabolic rewiring, and the horizontal transfer of bioactive cargo via adipocyte-derived extracellular vesicles, and adipocyte-mediated remodeling of the TME. Furthermore, we highlight noncanonical roles such as direct organelle donation, lipid-mediated drug sequestration, the enhancement of DNA repair pathways, and the activation of cell adhesion-dependent survival signaling. We also synthesize recent technological advancements employed to interrogate the intricate adipocyte-cancer interaction. Finally, we discuss emerging therapeutic strategies aimed at disrupting the adipocyte-cancer axis, while critically addressing the translational limitations of these interventions in clinical settings, offering a roadmap for integrating metabolic and anti-inflammatory interventions with standard regimens to overcome adipocyte-driven resistance and advance precision oncology.

Key Words: Adipocyte-cancer cell interaction, Therapy Resistance, Paracrine signaling, Metabolic reprogramming, Tumor Microenvironment remodeling

INTRODUCTION

The emergence of therapy resistance remains one of the most formidable challenges in cancer therapy. Despite remarkable advances in anticancer therapeutics including chemotherapy, molecularly targeted agents, and immunotherapies, most tumors eventually acquire resistance, leading to treatment failure and disease relapse (Bukowski *et al.*, 2020; Vasan *et al.*, 2019). This persistent problem underscores the urgent need to unravel the multifaceted mechanisms that enable tumor cells to survive and adapt under therapeutic pressure.

Over the past few decades, it has become increasingly evident that therapy resistance is not merely a cell-intrinsic phenomenon. Rather, it is profoundly influenced by the tumor microenvironment (TME), which functions as a dynamic ecosystem. In this environment, various stromal and immune con-

stituents, such as fibroblasts, immune cells, endothelial cells, and adipocytes interact with cancer cells to mediate survival and drug evasion (Bejarano *et al.*, 2021). Among these stromal constituents, adipocytes have emerged as active contributors to tumor progression and therapeutic resistance, particularly in malignancies that develop in adipose-rich environments, such as breast, ovarian, and pancreatic cancers (Wu *et al.*, 2019; Yang *et al.*, 2019). Epidemiological data consistently demonstrate that increased adiposity and visceral fat accumulation correlate with poorer responses to cancer therapies, suggesting a functional link between adipose tissue biology and cancer treatment outcomes (Litton *et al.*, 2008).

Advances in adipocyte biology have reshaped our understanding of these cells, revealing their active participation in tumor progression and therapy resistance. Rather than serving as passive lipid reservoirs, adipocytes communicate with cancer cells through a variety of mechanisms, including the

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secretion of a diverse secretome comprising adipokines and pro-inflammatory cytokines, lipid metabolite-mediated metabolic rewiring, the horizontal transfer of bioactive cargos via adipocyte-derived extracellular vesicles, and adipocyte-mediated TME remodeling (Cao, 2019). Beyond these established pathways, emerging evidence also highlights additional roles of adipocytes, such as the direct exchange of organelles, the sequestration-mediated modulation of local drug bioavailability, the augmentation of DNA repair systems, and the activation of cell adhesion-dependent survival signaling (Del Vecchio *et al.*, 2024; Kwak and Lee, 2023). These multifaceted interactions, both direct and indirect, collectively contribute to the development of resistance against diverse anticancer therapies (Piwocka *et al.*, 2024; Yao and He, 2021).

In this review, we summarize current knowledge on how adipocytes contribute to therapy resistance, delineate the key molecular mechanisms and noncanonical roles involved and highlight recent technological advancements for analyzing the intricate adipocyte–cancer interactome. Furthermore, we discuss emerging therapeutic strategies targeting this interaction, while critically addressing the translational limitations that must be overcome for successful clinical application.

CLINICAL EVIDENCE: ADIPOSE TISSUE AS A DETERMINANT OF THERAPY FAILURE

While the correlation between adipose tissue accumulation and increased mortality in cancer patients has long been established, emerging evidence suggests that this survival disparity is fundamentally driven by fat-mediated impairments in therapeutic efficacy. Large-scale meta-analyses, including the study of six million patients by Petrelli *et al.* demonstrate that a high BMI (≥ 30 kg/m²) significantly elevates the risk of recurrence and cancer-specific mortality across major malignancies, notably breast and colorectal cancers (Petrelli *et al.*, 2021). Crucially, this poor prognosis is increasingly recognized as a direct consequence of compromised treatment response rather than a mere reflection of baseline comorbidities. For instance, in neoadjuvant settings, obese patients consistently demonstrate lower pathological complete response (pCR) rates, suggesting that the adipose-rich environment, which is characterized primarily by visceral adiposity, acts as a pharmacological and biological sanctuary for resistant clones (Takabe *et al.*, 2012; Wang *et al.*, 2021a). These clinical observations are mechanistically driven by systemic endocrine dysregulation, specifically the insulin/IGF-1 signaling axis and an elevated leptin-to-adiponectin ratio, which collectively promote a pro-survival phenotype in cancer cells, thereby elevating the threshold for cell death under therapeutic stress (VanSaun, 2013; Zhang *et al.*, 2021).

As precision oncology advances, attention has shifted from overall adiposity toward the qualitative and spatial characteristics of adipose tissue as more informative predictors of treatment response. BMI often fails to capture the biological activity of specific fat depots, highlighting adipose tissue heterogeneity as an additional layer of complexity in adipocyte-driven therapy resistance (Schoettl *et al.*, 2018; Wang *et al.*, 2022a). Adipocytes derived from distinct anatomical depots exhibit substantial differences in metabolic activity, inflammatory signaling, and secretory profiles. In particular, visceral adipose tissue (VAT), including omental and other intra-ab-

dominal depots, displays a markedly pro-inflammatory phenotype compared with subcutaneous adipose depots. VAT is characterized by increased secretion of cytokines such as IL-6 and TNF- α as well as adipokines including leptin, which collectively activate oncogenic signaling pathways such as JAK/STAT3 and NF- κ B in adjacent tumor cells, ultimately promoting epithelial–mesenchymal transition (EMT), maintenance of cancer stem-like properties, and resistance to therapy (Cao, 2019; Gyamfi *et al.*, 2018; Ibrahim, 2010; Ouchi *et al.*, 2011). In contrast, subcutaneous adipose tissue (SAT) generally exhibits lower inflammatory cytokine production and a greater capacity for lipid storage, enabling relatively healthier adipose tissue expansion with reduced inflammatory stress (Schoettl *et al.*, 2018). Preferential fat accumulation in subcutaneous depots has therefore been associated with more favorable metabolic profiles and reduced metabolic risk compared with visceral adiposity (Tchkonina *et al.*, 2013). These depot-specific biological differences highlight the functional diversity of adipose tissue and suggest that VAT may act as a more potent mediator of tumor-promoting inflammation and therapy resistance than subcutaneous adipose tissue.

Consistent with these biological distinctions, visceral adiposity has been associated with reduced efficacy of anticancer therapies compared with subcutaneous fat accumulation, highlighting its potential role as a clinical indicator of therapy resistance. In patients receiving cytotoxic chemotherapy, increased VAT volume predicts poorer objective response rates and accelerated disease progression more accurately than total adiposity alone (Lee *et al.*, 2015; Yoshida and Fujiwara, 2023). Providing a mechanistic basis for these observations, O'Connell *et al.* recently demonstrated that chemoradiotherapy can remodel the adipose secretome toward a pro-inflammatory phenotype, which enhances mitochondrial reserve capacity in surviving tumor cells and ultimately promotes therapy resistance (O'Connell *et al.*, 2025).

Collectively, these clinical insights necessitate a paradigm shift in our understanding of adipose tissue, which should be redefined as an active 'regulatory organ' that modulates the pharmacodynamics and efficacy of anticancer agents. Rather than serving as a passive reservoir, this tissue functions as a central metabolic-immune hub that dictates the success of modern oncological interventions. Such a clinical reality underscores the urgency of exploring the specific molecular mechanisms through which adipocytes shield cancer cells, as detailed in the subsequent sections (Fig. 1).

ADIPOCYTE-DERIVED SECRETOME IN THERAPY RESISTANCE

Adipocytes function as highly active endocrine and inflammatory units, discharging a sophisticated array of signaling molecules known collectively as the secretome into the TME. Beyond their role as lipid reservoirs, these cells act as potent sources of diverse adipokines and pro-inflammatory cytokines that play pivotal roles in modulating the efficacy of anticancer therapies. Adipokines, a specialized class of cell-signaling proteins primarily derived from adipocytes, have emerged as critical regulators of therapy responsiveness through their distinct molecular pathways. A diverse array of adipokines, including leptin, resistin, visfatin, lipocalin-2, along with pro-inflammatory cytokines such as IL-6 and TNF- α , have been identified

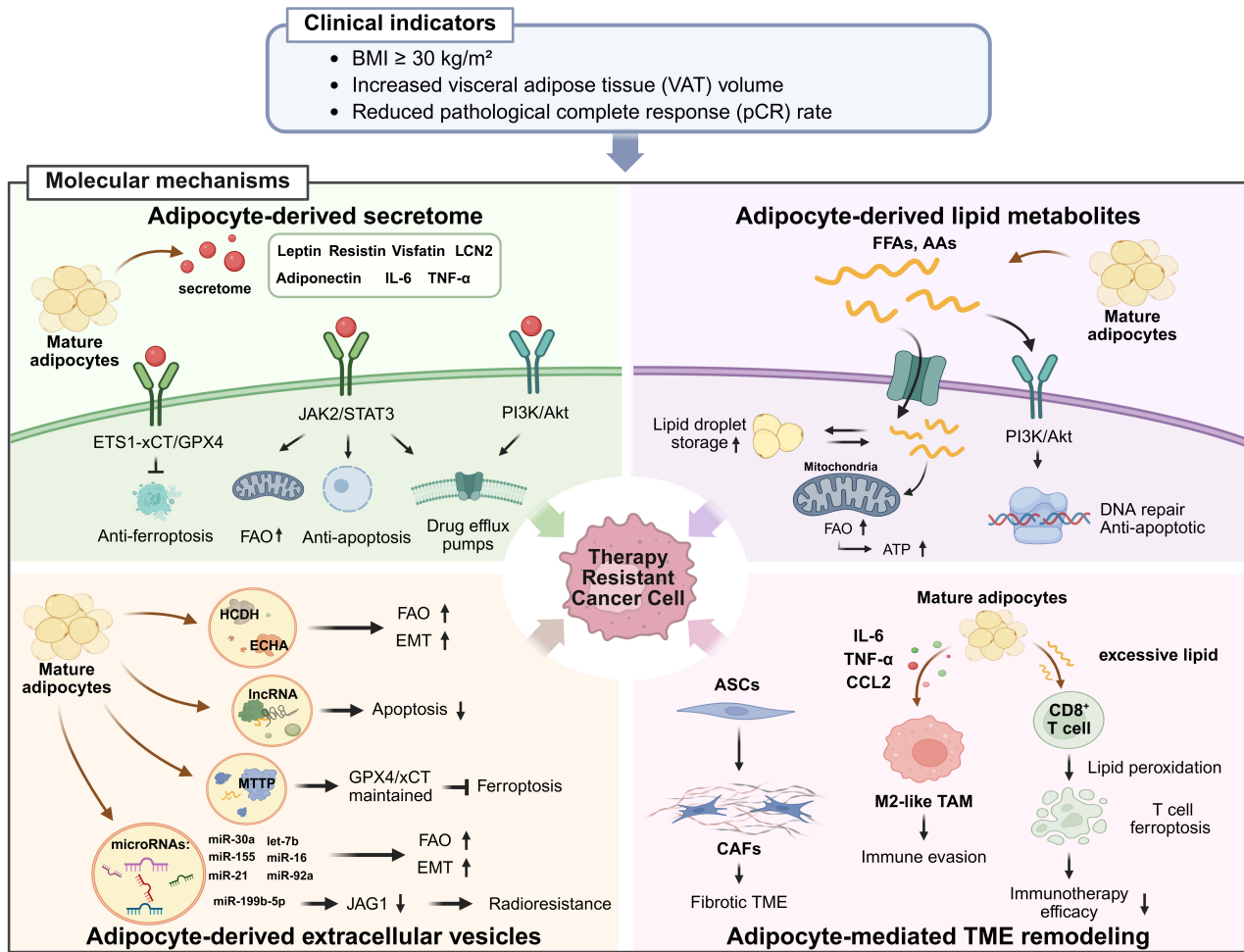


Fig. 1. Molecular mechanisms of adipocyte-mediated cancer therapy resistance and associated clinical indicators. Obesity-associated adipocytes significantly contribute to the development of therapy resistance in cancer cells through diverse molecular pathways, which are reflected in specific clinical indicators such as elevated BMI (≥ 30 kg/m²), increased visceral adipose tissue (VAT) volume, and reduced pathological complete response (pCR) rates. This figure illustrates four primary mechanisms: (1) Adipocyte-derived secretome, (2) Adipocyte-derived lipid metabolites, (3) Adipocyte-derived extracellular vesicles, and (4) Adipocyte-mediated TME remodeling.

as key mediators that actively promote pharmacological resistance within the TME. In contrast to these predominantly pro-tumorigenic factors, adiponectin was initially regarded as tumor suppressive, subsequent studies have revealed its dual role, promoting resistance in a tumor- and context-dependent manner. The accumulation of these findings highlights the multidimensional contribution of adipocyte-derived secreted factors to therapy resistance in cancer (Table 1).

Leptin

Originally recognized as a canonical satiety hormone responsible for regulating energy homeostasis and appetite through hypothalamic pathway, leptin has progressively emerged as a pivotal adipokine driving therapy resistance across diverse malignancies. Early evidence indicated that glioblastoma subtypes with elevated leptin receptor (ObR) expression exhibit pronounced resistance to temozolomide, a phenomenon attributed to STAT3 activation and subsequent upregulation of pluripotency factors SOX2 and OCT4, which

sustain cancer stem-like properties (Han *et al.*, 2013). Building upon this framework, subsequent studies revealed that in breast cancer stem cells, leptin activates the JAK2/STAT3–CPT1B signaling axis to enhance fatty acid oxidation (FAO), thereby reinforcing cellular survival and ultimately promoting resistance to paclitaxel and cisplatin (Wang *et al.*, 2018). In the context of pancreatic cancer, leptin induces the expression of miR-342-3p, which directly targets the 3'-UTR of the tumor suppressor KLF6, enabling the evasion of gemcitabine-induced apoptosis and promoting chemoresistance (Ma *et al.*, 2019). Consistently, leptin facilitates gemcitabine chemoresistance in gallbladder cancer through the STAT3–CEBPD signaling axis, upregulating MCL1 to enhance mitochondrial fusion and maintain cellular survival under therapeutic pressure (Wang *et al.*, 2021b). Furthermore, hyperleptinemia associated with obesity promotes 5-fluorouracil chemoresistance in colorectal cancer. This effect is mediated through AMPK–LATS1 inhibition, YAP/TEAD-driven AXL upregulation, and subsequent P-glycoprotein-mediated drug efflux (Chen *et*

Table 1. Recently identified adipokine-mediated mechanisms of therapy resistance

Adipokine	Cancer type	Mechanism	Reference
Leptin	Glioblastoma	Activates STAT3 to upregulate SOX2 and OCT4, thereby sustaining cancer stem-like properties and temozolomide resistance	Han <i>et al.</i> , 2013
	Breast	Stimulates the JAK2/STAT3–CPT1B axis to enhance fatty acid oxidation (FAO), promoting resistance to paclitaxel and cisplatin	Wang <i>et al.</i> , 2018
Resistin	Pancreatic	Induces miR-342-3p to target the 3'-UTR of KLF6, enabling evasion of gemcitabine-induced apoptosis	Ma <i>et al.</i> , 2019
	Gallbladder	Activates the STAT3–CEBPD–MCL1 axis to enhance mitochondrial fusion and maintain survival against gemcitabine	Wang <i>et al.</i> , 2021b
	Colorectal	Inhibits AMPK–LATS1 to drive the YAP/TEAD–AXL–P-gp efflux axis, promoting 5-FU resistance	Chen <i>et al.</i> , 2021
	Breast	Promotes M2-IL-8 TAM polarization to create a docetaxel-resistant immune microenvironment	Gao <i>et al.</i> , 2024
	Breast	Activates the AMPK/mTOR axis to induce autophagy, enabling evasion of doxorubicin-induced apoptosis	Liu <i>et al.</i> , 2017
Visfatin	Multiple Myeloma	Suppresses caspase-mediated apoptosis and upregulates ABCB1 and ABCC1 transporters to drive multidrug resistance	Pang <i>et al.</i> , 2017
	Melanoma	Enhances Caveolin-1 stability and P-gp transcription to attenuate dacarbazine efficacy in obese models	Malvi <i>et al.</i> , 2018
LCN2	Colorectal	Amplifies inflammatory survival signaling to promote 5-FU resistance	Lee <i>et al.</i> , 2022
	NSCLC/Colorectal	Increases ABCC1 expression via Akt signaling and triggers NF-κB p65–dependent MDR1 transcription to reduce doxorubicin accumulation	Cao <i>et al.</i> , 2017
Visfatin	Colorectal	Activates the SDF-1/CXCR4–Akt survival pathway to resist 5-FU	Yan <i>et al.</i> , 2017
	Colorectal	Amplifies the AREG–EGFR–JNK/p38–STAT3 axis to reduce 5-FU sensitivity	Zhao <i>et al.</i> , 2022
	Colorectal	Suppresses ferroptosis by reducing intracellular labile iron and enhancing the ETS1–xCT/GPX4 antioxidant axis, conferring 5-FU resistance	Huang <i>et al.</i> , 2024
TNF-α	NSCLC	Forms a complex with MMP-9 to attenuate drug-induced apoptosis and suppress pyroptosis via inhibition of GSDMD and GSDME cleavage	Chaudhary <i>et al.</i> , 2021
	Cervical	Interacts with lncRNA TMPO-AS1 to promote ferroptosis resistance, attenuating the efficacy of ferroptosis-inducing agents such as sulfasalazine	Shi <i>et al.</i> , 2024
Adiponectin	Glioblastoma	Activates the Akt–mTOR signaling pathway to enhance temozolomide chemoresistance	Ju <i>et al.</i> , 2025
	Breast	Preserves the CD44 ⁺ /CD24 [−] /ALDH1 ⁺ stem-like subpopulation and maintains mitochondrial stability to evade tamoxifen-induced apoptosis	Sun <i>et al.</i> , 2025
IL-6	Breast	Binds to receptors to activate the JAK2/STAT3 cascade, promoting EMT and the acquisition of therapy-tolerant phenotypes	Naimo <i>et al.</i> , 2025
	Breast	Amplifies tumor-derived CXCL1 to establish a STAT3/NF-κB feed-forward circuit, increasing MMP7/9 for stromal remodeling and MDR	Gyamfi <i>et al.</i> , 2018
TNF-α	General	Paradoxically fosters survival via chronic low-level exposure, bolstering anti-apoptotic and antioxidant gene expression through NF-κB	Ruan <i>et al.</i> , 2025
	HCC, Melanoma	Acts in concert with IL-6 to activate NF-κB and STAT3, upregulating PD-L1 to attenuate T-cell-mediated immunity and ICB response	Guo <i>et al.</i> , 2024; Wang and Lin, 2008
TNF-α	HCC, Melanoma	Acts in concert with IL-6 to activate NF-κB and STAT3, upregulating PD-L1 to attenuate T-cell-mediated immunity and ICB response	Li <i>et al.</i> , 2020

Table 1 summarizes the multifaceted molecular mechanisms through which adipocyte-derived secretome components, including specific adipokines and cytokines, orchestrate therapy resistance across various malignancies. These interactions involve diverse signaling pathways, metabolic rewiring, and the modulation of the tumor microenvironment to shield cancer cells from therapeutic stress. STAT3, Signal Transducer and Activator of Transcription 3; SOX2, SRY-Box Transcription Factor 2; OCT4, Octamer-binding Transcription Factor 4; JAK2, Janus Kinase 2; CPT1B, Carnitine Palmitoyltransferase 1B; FAO, Fatty Acid Oxidation; KLF6, Kruppel-like Factor 6; CEBPD, CCAAT/Enhancer Binding Protein Delta; MCL1, Myeloid Cell Leukemia 1; AMPK, Adenosine Monophosphate-activated Protein Kinase; LATS1, Large Tumor Suppressor Kinase 1; YAP, Yes-associated Protein; TEAD, TEA Domain Transcription Factor; AXL, AXL Receptor Tyrosine Kinase; P-gp, P-glycoprotein; 5-FU, 5-Fluorouracil; IL-8, Interleukin 8; TAM, Tumor-associated Macrophage; mTOR, Mammalian Target of Rapamycin; ABCB1, ATP-binding Cassette Subfamily B Member 1; ABCC1, ATP-binding Cassette Subfamily C Member 1; NSCLC, Non-small Cell Lung Cancer; MDR1, Multidrug Resistance Protein 1; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of Activated B cells; SDF-1, Stromal Cell-derived Factor 1; CXCR4, C-X-C Chemokine Receptor Type 4; AREG, Amphiregulin; EGFR, Epidermal Growth Factor Receptor; JNK, c-Jun N-terminal Kinase; CREB, cAMP Response Element-binding Protein; ETS1, Protein C-ets-1; xCT, Cystine/Glutamate Antiporter; GPX4, Glutathione Peroxidase 4; MMP7/9, Matrix Metalloproteinase 7/9; GSDMD/GSDME, Gasdermin D/Gasdermin E; lncRNA, Long Non-coding RNA; TMPO-AS1, Thymopoietin Antisense RNA 1; ALDH1, Aldehyde Dehydrogenase 1; IL-6, Interleukin 6; EMT, Epithelial–mesenchymal Transition; CXCL1, C-X-C Motif Chemokine Ligand 1; MDR, Multidrug Resistance; TNF-α, Tumor Necrosis Factor-α; PD-L1, Programmed Death-ligand 1; HCC, Hepatocellular Carcinoma; ICB, Immune Checkpoint Blockade.

et al., 2021). More recently, the immunomodulatory capacity of leptin was highlighted in triple-negative breast cancer (TNBC), where leptin-mediated activation of tumor-associated macrophages (TAMs) promotes M2 polarization with increased IL-8 secretion, ultimately fostering docetaxel chemoresistance (Gao *et al.*, 2024). Collectively, these findings establish leptin as a multifaceted modulator of therapy resistance across multiple malignancies, operating through the enhancement of cancer stemness, metabolic rewiring, and the perturbation of epigenetic and immune-regulatory landscapes.

Resistin

While resistin was initially characterized by its role in obesity-induced insulin resistance (Steppan *et al.*, 2001), emerging evidence has expanded its functional repertoire to include the promotion of chemoresistance in various malignancies. Early studies in breast cancer models demonstrated that resistin activates the AMPK/mTOR axis to induce autophagy, thereby enabling tumor cells to evade doxorubicin-induced apoptosis (Liu *et al.*, 2017). In parallel, work in multiple myeloma revealed that resistin suppressed caspase-mediated apoptosis and upregulated the drug efflux transporters ABCB1 and ABCC1, driving multidrug resistance (Pang *et al.*, 2017). In obese melanoma models, resistin has been shown to act in concert with leptin to significantly attenuate the therapeutic efficacy of dacarbazine. Mechanistically, resistin enhances the protein expression of caveolin-1 by increasing its stability and elevates the transcriptional levels of P-glycoprotein (P-gp), a critical ATP-binding cassette (ABC) transporter involved in multidrug efflux (Malvi *et al.*, 2018). Moreover, the impact of resistin extended beyond cell-intrinsic mechanisms to encompass remodeling of the TME. Most recently, a study on colorectal cancer demonstrated that resistin confers resistance to 5-fluorouracil (5-FU) by triggering the TLR4-mediated ERK signaling pathway, which subsequently induces the increase of the NLRP3 expression. This resistin-driven inflammatory axis provides a survival advantage to malignant cells, further illustrating how adipocyte-derived factors orchestrate complex intracellular networks to bypass cytotoxic insults (Lee *et al.*, 2022). These findings underscore the ability of resistin to integrate metabolic and inflammatory networks in fostering therapy resistance.

Visfatin

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT), is a rate-limiting enzyme in the nicotinamide adenine dinucleotide (NAD⁺) salvage pathway that primarily regulates cellular energy metabolism and redox homeostasis. Beyond its fundamental metabolic role, visfatin has been increasingly implicated in cancer therapy resistance, acting through both metabolic regulation and the modulation of signaling pathways that sustain survival and therapeutic evasion (Navas and Carnero, 2021). Its role in orchestrating transporter-based resistance was initially highlighted by findings that visfatin increases ABCC1 expression via Akt signaling and triggers NF- κ B p65-dependent MDR1 transcription, collectively reducing the intracellular accumulation of doxorubicin (Cao *et al.*, 2017; Yan *et al.*, 2017). Expanding on these findings, recent work in colorectal cancer models has demonstrated that visfatin activates the SDF-1/CXCR4–Akt axis to upregulate anti-apoptotic factors such as Bcl-2 and survivin while suppressing Bax and p53, thereby facilitating the acqui-

sition of resistance to 5-FU (Zhao *et al.*, 2022). Furthermore, visfatin has been shown to strengthen EGFR signaling by inducing amphiregulin (AREG) expression through the JNK/p38–STAT3/CREB transcriptional cascade, which significantly diminishes 5-FU sensitivity in malignant cells (Huang *et al.*, 2024).

Lipocalin-2

Lipocalin-2 (LCN2), originally identified as a regulator of iron metabolism and inflammation, has more recently been recognized as an atypical adipokine that contributes to therapy resistance. In colorectal cancer, overexpression of LCN2 suppresses ferroptosis by reducing intracellular labile iron and enhancing the ETS1–xCT/GPX4 antioxidant axis, thereby promoting tumor progression and conferring 5-FU chemoresistance (Chaudhary *et al.*, 2021). In non-small cell lung cancer (NSCLC), it has been identified as a critical mediator of acquired resistance to third-generation EGFR TKIs. Mechanistically, LCN2 forms a stable complex with MMP-9, shielding it from enzymatic degradation and enhancing its pro-tumorigenic activity. This LCN2–MMP-9 axis facilitates therapeutic evasion by simultaneously attenuating drug-induced apoptosis and suppressing pyroptosis through the inhibition of GSDMD and GSDME cleavage (Shi *et al.*, 2024). In cervical cancer, the lncRNA TMPO-AS1 promotes tumorigenesis and ferroptosis resistance by interacting with LCN2, thereby attenuating the efficacy of ferroptosis-inducing agents such as sulfasalazine and ultimately contributing to a therapy-resistant phenotype (Ju *et al.*, 2025).

Adiponectin

Adiponectin is a pleiotropic adipokine primarily known for its role in enhancing insulin sensitivity and exerting systemic anti-inflammatory effects. Unlike other adipokines, adiponectin was initially regarded as a protective adipokine, as it was reported to promote apoptosis through activation of the AMPK and p38 MAPK pathways (Dieudonne *et al.*, 2006). However, accumulating evidence has revealed its dual role in cancer therapy resistance. For example, in glioblastoma, adiponectin activates the Akt–mTOR signaling pathway to enhance temozolomide chemoresistance (Sun *et al.*, 2025), while in tamoxifen-resistant breast cancer cells, it selectively preserves the CD44⁺/CD24[−]/ALDH1⁺ stem-like subpopulation and maintains mitochondrial stability, thereby promoting apoptosis evasion and sustaining therapy resistance (Naimo *et al.*, 2025). These findings indicate that the impact of adiponectin is highly context-dependent, often transitioning from a protective agent to a resistance-promoting factor by sustaining cancer stemness and survival signaling.

IL-6

The role of interleukin-6 (IL-6) as a potent driver of anticancer drug resistance has been extensively documented over several decades (Morteza and Amirhossein, 2016). While tumor cells themselves can increase IL-6 expression in response to extrinsic stimuli, adipocytes within the TME serve as a critical exogenous source of this cytokine. In particular, cancer-associated adipocytes (CAAs) function as potent secretory hubs that discharge a diverse array of pro-inflammatory cytokines, with IL-6 emerging as a central mediator linking obesity-associated chronic inflammation to therapy resistance. The clinical relevance of adipocyte-derived IL-6

has been underscored in human breast cancer tissues, where its upregulation within the TME correlates with poor therapeutic outcomes (Ahmad *et al.*, 2017). Mechanistically, IL-6 released from mature adipocytes binds to its receptor complex on adjacent tumor cells, activating the JAK2/STAT3 signaling cascade. This activation promotes epithelial–mesenchymal transition (EMT) and drives the acquisition of invasive and therapy-tolerant phenotypes (Gyamfi *et al.*, 2018). In TNBC, adipocyte-secreted IL-6 amplifies tumor-derived CXCL1 production, establishing a reciprocal STAT3/NF- κ B feed-forward circuit. This circuit enhances the expression of MMP7 and MMP9, facilitating stromal remodeling and creating an inflammatory niche conducive to multidrug resistance (Ruan *et al.*, 2025).

TNF- α

Tumor necrosis factor- α (TNF- α) is another cornerstone of the adipocyte-derived secretome that promotes malignant progression. While traditionally recognized for its role in acute inflammation and apoptosis induction, chronic exposure to low-level TNF- α within the TME has been shown to paradoxically foster tumor survival and therapeutic resistance (Zhao *et al.*, 2021). This pro-survival effect is primarily mediated through TNF- α -induced NF- κ B activation, which bolsters the expression of anti-apoptotic genes and antioxidant enzymes, thereby neutralizing the pro-apoptotic effects of conventional chemotherapies (Guo *et al.*, 2024; Wang and Lin, 2008). Beyond this intrinsic drug resistance, adipocyte-derived TNF- α acts in concert with IL-6 to activate NF- κ B and STAT3 signaling, leading to the upregulation of PD-L1 expression in malignancies such as hepatocellular carcinoma and melanoma. This process attenuates cytotoxic T-cell-mediated immunity and creates an immunosuppressive microenvironment that diminishes responsiveness to immune checkpoint blockade (Li *et al.*, 2020). These findings emphasize that TNF- α acts as a dual-edged sword in the TME, where its sustained secretion from adipocytes orchestrates both cell-intrinsic survival and extrinsic immune subversion.

ADIPOCYTE-DERIVED LIPID METABOLITE-MEDIATED THERAPY RESISTANCE

Early studies established the conceptual framework that adipocytes act as active supporters of tumor progression by supplying fatty acids and metabolic fuels within the TME. These adipocyte-derived lipid metabolites serve as a critical energy reservoir that sustains tumor growth and aggressive phenotypes by maintaining metabolic homeostasis and providing raw materials for biomass synthesis (Cao, 2019). In colon cancer, adipocytes release free fatty acids (FFAs) that drive mitochondrial FAO and autophagy, thereby enabling cancer cell survival under nutrient-deprived conditions (Wen *et al.*, 2017). In acute monocytic leukemia, bone marrow adipocytes (BMAs) deliver fatty acids that activate AMPK signaling and reprogram transcriptional networks to preserve metabolic equilibrium (Tabe *et al.*, 2017). Similarly, in breast cancer, adipocyte-derived fatty acids accumulate as intracellular triglycerides and are subsequently mobilized via ATGL-dependent lipolysis to fuel FAO, a metabolic remodeling process that promotes invasion and metastasis (Wang *et al.*, 2017). Collectively, these findings reveal a unifying mechanism in which the

uptake of adipocyte-derived fatty acids potentiates oxidative metabolism, thereby reinforcing tumor growth, survival, and adaptive resilience to metabolic stress.

Expanding upon this conceptual groundwork, more recent investigations have moved beyond descriptive observations to delineate explicit mechanisms by which adipocyte-derived lipid metabolites and FAO directly contribute to therapy resistance. In acute myeloid leukemia (AML), BMA provide free fatty acids that fuel mitochondrial FAO, thereby reducing reactive oxygen species (ROS) accumulation and maintaining Bcl-2-mediated survival pathways, which collectively diminish cytarabine-induced cytotoxicity (Tabe *et al.*, 2018). In a related hematologic context, a co-culture study of acute lymphoblastic leukemia (ALL) demonstrated that leukemia cells induce adipocytes to release free fatty acids. These fatty acids are subsequently taken up by ALL cells and either stored in lipid droplets or utilized as fuel for mitochondrial FAO. This metabolic adaptation allows ALL cells to bypass glucose dependency and maintain ATP production, thereby evading chemotherapy-induced apoptosis, with unsaturated fatty acids identified as critical drivers of this resistance (Tucci *et al.*, 2021; Yang *et al.*, 2019). Similarly, in ovarian cancer, adipocyte-secreted arachidonic acid (AA) has been shown to activate the PI3K/Akt pathway, strengthening DNA repair and anti-apoptotic signaling while simultaneously augmenting FAO to blunt cisplatin-induced apoptosis (Yang *et al.*, 2019). Together, these findings highlight a unifying mechanism whereby adipocyte-derived fatty acids serve as fuel for FAO-driven oxidative metabolism, conferring a survival advantage against diverse chemotherapeutic insults.

ADIPOCYTE-DERIVED EXTRACELLULAR VESICLES IN THERAPY RESISTANCE

Extracellular vesicles (EVs) serve as pivotal mediators of intercellular communication within the TME by delivering molecular cargos—including proteins, lipids, and various RNA species—that fundamentally remodel recipient cell phenotypes (Becker *et al.*, 2016). Adipocyte-derived EVs, in particular, exploit this mechanism to transport specific miRNAs, fatty acids, and metabolic enzymes that reprogram tumor signaling and metabolism, thereby establishing a permissive niche for disease progression and therapeutic evasion (Zhou *et al.*, 2023).

Early studies established that adipocyte-derived EVs prime cancer cells for survival by driving aggressive metabolic and phenotypic adaptations. These vesicles deliver key FAO enzymes (e.g., ECHA, HCDH) and regulatory miRNAs (e.g., miR-155, miR-30a) that reprogram mitochondrial bioenergetics and promote EMT (La Camera *et al.*, 2021; Lazar *et al.*, 2016; Liu *et al.*, 2023). Rather than mere phenotypic shifts, these adaptations function as a metabolic safeguard, enhancing mitochondrial reserve capacity and cytoskeletal plasticity to shield tumor cells from subsequent therapeutic insults.

Building upon this metabolic foundation, recent evidence underscores the direct role of adipocyte-derived EVs in coordinating multifaceted drug resistance. Beyond metabolic fueling, these vesicles serve as vehicles for complex epigenetic and anti-ferroptotic mechanisms that shield tumor cells against oxidative and therapeutic stress. A representative example of this epigenetic modulation is observed in multiple myeloma,

where BMA-derived exosomes are enriched with long non-coding RNAs (lncRNAs) that undergo METTL7A-mediated m⁶A methylation. Once delivered into myeloma cells, these exosomal lncRNAs interact with epigenetic regulators such as EZH2 to suppress the expression of apoptosis-related genes, thereby blocking bortezomib-induced cell death and promoting chemoresistance (Wang *et al.*, 2022b). In ovarian cancer, omental adipocyte-derived exosomes deliver miR-21, let-7b, miR-16, and miR-92a to tumor cells, promoting EMT and diminishing paclitaxel sensitivity (Williams *et al.*, 2024). Consistently, adipocyte-derived EVs have been shown to deliver microsomal triglyceride transfer protein (MTTP) into colorectal cancer cells, where MTTP engages with PRAP1 to repress ZEB1 expression while sustaining GPX4 and xCT (SLC7A11) levels. This molecular cascade attenuates lipid ROS accumulation and suppresses ferroptosis (Zhang *et al.*, 2022).

Beyond drug resistance, adipocyte-derived EVs have also been implicated in mediating radioresistance. EVs secreted from adipocytes are enriched in miR-199b-5p, which is transferred into colorectal cancer cells and directly binds to the 3'-UTR of JAG1 to repress its expression. Although the precise mechanisms by which JAG1 regulates the radiation response remain to be fully elucidated, these findings establish adipocyte-derived exosomal miR-199b-5p as a critical mediator of colorectal cancer radioresistance through the suppression of JAG1 (Lv *et al.*, 2024). Together, these findings position adipocytes as key modulators of tumor behavior, extending their influence from metabolic reprogramming to the direct induction of drug resistance. By demonstrating that adipocyte-derived EVs actively sustain therapy-resistant phenotypes, these studies collectively underscore adipocyte–cancer cell interactions as critical therapeutic targets.

ADIPOCYTE-MEDIATED STROMAL AND IMMUNE REMODELING IN THERAPY RESISTANCE

Beyond direct metabolic and paracrine signaling, adipocytes exert a profound influence on the TME by regulating the remodeling of stromal and immune compartments, which ultimately dictates the efficacy of anticancer therapies, including immune checkpoint inhibitors. Emerging evidence suggests that adipocyte-derived cues fundamentally reshape the surrounding milieu, establishing a fibrotic and immunosuppressive niche that pre-conditions the tumor for sustained therapeutic resistance.

Under tumor-derived stimuli, adipocyte stem cells (ASCs) can transdifferentiate into cancer-associated fibroblast (CAF)-like cells, characterized by increased α -SMA and collagen I expression and enhanced secretion of pro-invasive cytokines and matrix-remodeling enzymes (El Alaa *et al.*, 2024). Importantly, these ASC-derived CAFs also suppress immune-cell activity, thereby promoting tumor invasion and metastasis. Although direct evidence connecting this process to therapy resistance remains limited, adipocyte-driven fibroblast activation and immune suppression collectively establish a fibrotic and immunoregulatory microenvironment that primes the tumors for acquired therapeutic resistance.

In parallel, adipocyte–macrophage crosstalk contributes an additional immunomodulatory layer. Adipocyte-secreted IL-6, TNF- α , and CCL2 polarize macrophages toward an M2-like tumor-associated phenotype, which in turn enhances adipo-

cyte lipolysis and cytokine release. This self-perpetuating inflammatory loop promotes stromal remodeling, immune evasion, and tumor progression, thereby creating a permissive context for reduced therapy responsiveness (Correa *et al.*, 2017). Furthermore, recent studies have identified a metabolic axis of immune suppression, wherein excessive lipids released from adipocytes are internalized by CD8⁺ T cells, triggering lipid peroxidation and subsequent ferroptosis. This adipocyte-induced ferroptotic cell death impairs the effector function of infiltrating T cells, thereby undermining the efficacy of T cell-based immunotherapies (Dalangood *et al.*, 2025; Ma *et al.*, 2021).

Consistent with these findings, recent experimental work has demonstrated a direct mechanistic link between adipocyte-induced TME remodeling and therapy resistance. In bone metastasis, BMAs induce α -SMA⁺ CAFs and suppress CD8⁺ T-cell infiltration, resulting in enhanced invasion and chemoresistance (Sato *et al.*, 2023). Adipocyte-rich TMEs display transcriptional signatures of extracellular-matrix organization, TGF- β activation, and immune checkpoint upregulation, confirming that adipocyte-mediated stromal and immune remodeling constitutes a critical foundation for therapy resistance. Collectively, these studies establish adipocytes as active architects of a fibrotic, inflammatory, and immunosuppressive TME that promotes tumor progression and undermines therapeutic efficacy.

EMERGING ROLES OF ADIPOCYTE IN THERAPY RESISTANCE

Recent studies have revealed several additional mechanisms through which adipocytes promote therapy resistance. One important route involves the direct transfer of organelles. Del Vecchio *et al.* demonstrated that ASCs deliver mitochondria to breast cancer cells via tunneling nanotubes (TNTs). These transferred mitochondria enhanced OXPHOS and ATP production within the recipient cells. This metabolic augmentation provides the necessary bioenergetic fuel to activate ATP-dependent ABC efflux pumps, which actively extrude cytotoxic agents and reduce intracellular drug accumulation. Consequently, this organelle-mediated metabolic reprogramming confers a robust survival advantage under chemotherapeutic pressure (Del Vecchio *et al.*, 2024).

Adipocytes can also modulate drug response by altering the effective drug concentration rather than cellular metabolism. In multiple myeloma, BMAs have been shown to absorb the lipophilic chemotherapeutic doxorubicin and sequester it within large lipid droplets. By acting as physical reservoirs for the drug, BMAs lower its bioavailability to tumor cells, thereby protecting them from DNA damage and apoptosis (Kwak and Lee, 2023).

Another layer of chemoresistance arises through the regulation of DNA repair pathways. Liang *et al.* reported that adipocyte-derived A1BG directly interacts with NAMPT, enhancing its protein stability and increasing NAD⁺ production. This, in turn, stimulates PARP1 activity and strengthens DNA repair capacity, ultimately diminishing the cytotoxic effects of cisplatin in osteosarcoma (Liang *et al.*, 2025).

Finally, adipocytes can enhance cell adhesion-dependent signaling to promote chemoresistance. Adipocytes derived from obese patients interact with multiple myeloma cells

through integrin $\beta 1$ -mediated adhesion, thereby inducing cell adhesion-mediated drug resistance. This adhesion signaling activates the FAK-PI3K/Akt survival pathway and suppresses apoptosis, while upregulating ATP-dependent efflux transporters (P-gp, MRP1), collectively reinforcing resistance to proteasome inhibitors such as bortezomib and lenalidomide (Ochiai *et al.*, 2023).

Altogether, these findings redefine adipocytes as multifaceted regulators of therapy resistance that transcend simple metabolic support. By coordinating a wide spectrum of noncanonical mechanisms, adipocytes establish a complex survival niche that necessitates novel therapeutic strategies targeting the adipocyte-cancer cell interactome.

NOVEL TECHNOLOGIES FOR DECIPHERING ADIPOCYTE-CANCER INTERACTIONS

Recent advances in high-resolution molecular profiling technologies have substantially transformed the capacity to investigate interactions between adipocytes and tumor cells within the TME. In particular, single-cell and single-nucleus RNA sequencing (sc/snRNA-seq) have revolutionized the systematic characterization of adipose tissue heterogeneity, revealing functionally distinct stromal, immune, and adipocyte precursor populations that drive tumor-associated inflammation and metabolic reprogramming (Norreen-Thorsen *et al.*, 2022; Vijay *et al.*, 2020). These advances in sequencing technology have uncovered previously unrecognized adipocyte subtypes and immune cell states, providing important insights into the molecular networks through which adipose tissue influences tumor progression and therapy resistance (Emont *et al.*, 2022). Furthermore, the development of multi-omics approaches integrating transcriptomic, epigenomic, and metabolomic features with these single-cell sequencing platforms has enabled more precise reconstruction of gene regulatory networks governing adipocyte-tumor interactions at the cellular level.

However, because tissue dissociation inherently disrupts spatial architecture, sc/snRNA-seq alone is insufficient to capture the context-dependent and proximity-driven interactions that define adipocyte-mediated signaling within the TME. To address this limitation, spatial transcriptomics has emerged as a complementary approach that preserves tissue architecture while mapping gene expression across tumor tissues (Keesling *et al.*, 2025). This approach enables reconstruction of spatially defined microenvironmental niches and proximity-dependent signaling networks shaped by adipocyte-tumor interactions (Massier *et al.*, 2023).

In parallel, various three-dimensional (3D) platforms have been developed to faithfully recapitulate the intricate crosstalk between adipocytes and tumor cells. In particular, spheroid-based co-culture models and scaffold-supported 3D matrices allow the investigation of adipose-tumor interactions within structurally complex environments compared with conventional two-dimensional monolayer cultures (Quan *et al.*, 2024; Strusi *et al.*, 2026). These systems reliably preserve key features of the tumor microenvironment, including cell-cell and cell-matrix interactions, extracellular matrix (ECM) remodeling, and diffusion gradients of oxygen, nutrients, and signaling molecules, all of which critically influence cellular phenotype, metabolic adaptation, and therapeutic response (Breslin and

O'Driscoll, 2013; Edmondson *et al.*, 2014).

Beyond traditional 3D cultures, organoid-based systems have emerged to more precisely mimic the structural organization and physiological complexity of adipose tissue. While initial models derived from human adipose stem cells or vascularized microvessel fragments focused on robustly recapitulating adipocyte differentiation and metabolic features more recent advances have introduced geometrically inverted mammary organoids and tumor-adipose assembloids to directly model malignant interactions (Mandl *et al.*, 2022; Strobel *et al.*, 2021). These sophisticated platforms generate spatially organized multicellular architectures that authentically capture tumor invasion and adipocyte-driven microenvironmental remodeling, thereby enabling detailed interrogation of the metabolic coupling between these cell types (Lei *et al.*, 2025; Mertz *et al.*, 2023).

Despite these advances, current models still face limitations in fully recapitulating native tissue architecture, and patient-derived adipose organoid systems remain underdeveloped. Addressing these limitations through integration with emerging technologies such as single-cell profiling and spatial transcriptomics is expected to substantially advance our mechanistic understanding of adipocyte-cancer interactions and facilitate the identification of therapeutic vulnerabilities associated with adipocyte-driven therapy resistance.

THERAPEUTIC STRATEGIES TO COUNTERACT ADIPOCYTE-DRIVEN RESISTANCE

Understanding the multifaceted mechanisms by which adipocytes drive therapy resistance provides a foundation for developing novel therapeutic strategies. These strategies can be broadly categorized into three complementary approaches: (1) blocking adipocyte-derived paracrine factors, (2) targeting metabolic energy coupling, and (3) reprogramming the inflammatory microenvironment. Each approach aims to disrupt the metabolic and signaling interdependence between adipocytes and tumor cells, thereby restoring sensitivity to anticancer therapies (Fig. 2, Table 2).

Blocking Adipocyte-Derived Paracrine Factors

Adipocytes release a spectrum of cytokines, growth factors, and adipokines that reactivate pro-survival signaling within the TME, necessitating the development of therapeutic strategies to neutralize these paracrine networks. In preclinical breast cancer models, IL-6 derived from adipocytes and infiltrating myeloid cells drives resistance to VEGF inhibition by maintaining dysfunctional vasculature, exacerbating hypoxia, and promoting an immunosuppressive microenvironment. Pharmacologic or genetic IL-6 blockade, such as with tocilizumab, restores sensitivity to anti-VEGF treatment in obese mice, normalizing vessel perfusion, alleviating hypoxia, and reducing tumor growth and metastasis. These findings position adipocyte-derived IL-6 as a key mediator of anti-VEGF resistance and support IL-6/IL-6R targeting as a rational strategy to overcome obesity-driven antiangiogenic therapy failure (Incio *et al.*, 2018).

Furthermore, adipocyte-cancer cell crosstalk significantly drives resistance to FGFR inhibitors like erdafitinib. Specifically, adipocyte precursors, but not differentiated adipocytes, secrete neuregulin-1 (NRG1) in paracrine manner and acti-

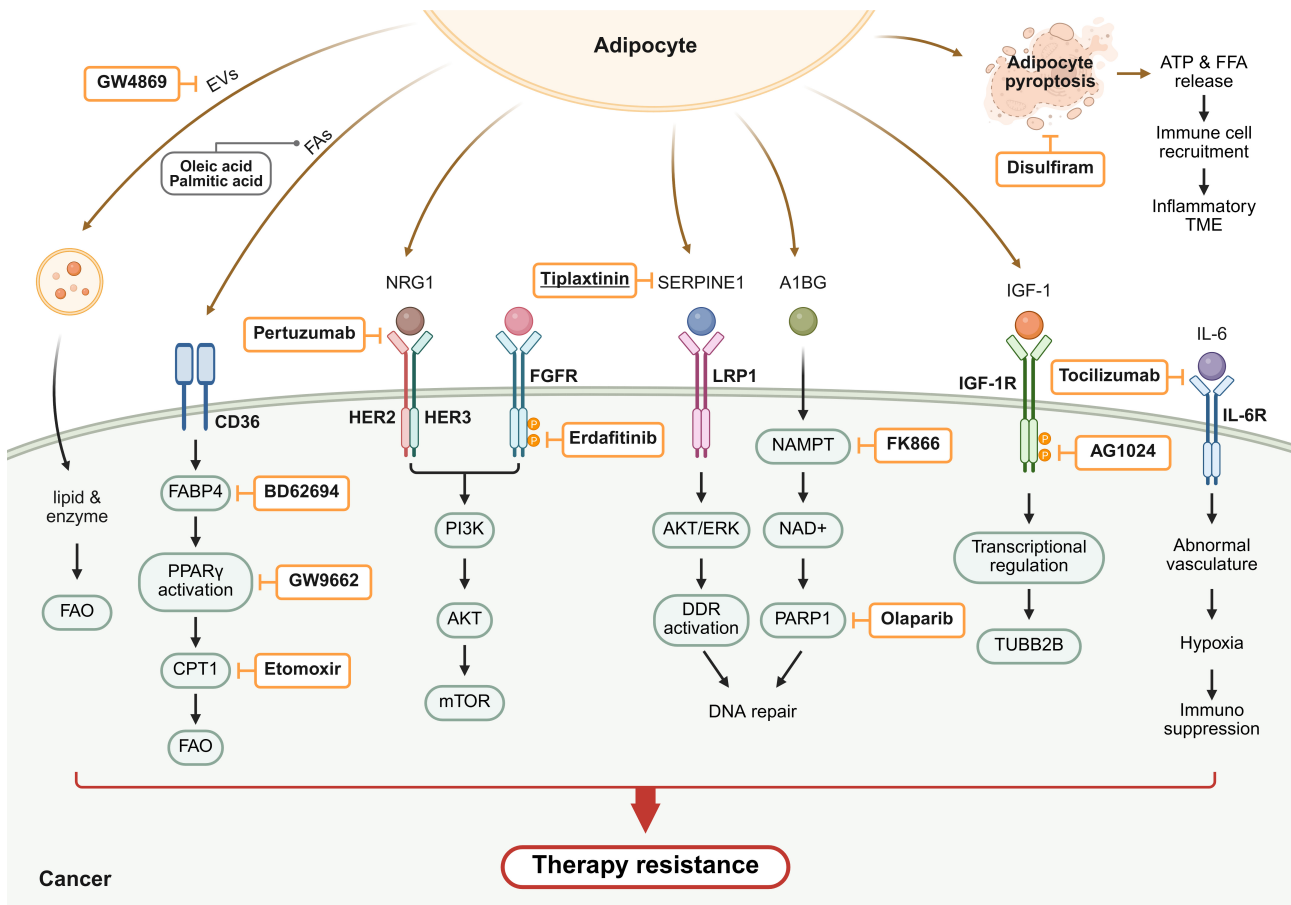


Fig. 2. Pharmacological strategies to overcome adipocyte-mediated therapy resistance by targeting adipocyte-cancer cell interactions. Diverse therapeutic strategies summarized in Table 2 are presented to intercept adipocyte-mediated survival signaling and restore treatment sensitivity.

vate HER3 (ERBB3) signaling in cancer cells. This activation bypasses FGFR blockade, providing an alternative survival route that leads to rapid acquired resistance. Notably, combinational treatment of pertuzumab to target the NRG1/HER3 axis effectively abolishes therapy resistance and restores erdafitinib sensitivity *in vitro* and *in vivo*. These findings suggest that combined FGFR and HER3 targeting is a potent clinical strategy to overcome the protective influence of the adipocytic niche in FGFR-driven malignancies (Hosni *et al.*, 2024).

Similarly, targeting the adipocyte-derived IGF-1 signaling axis represents a promising approach to restore sensitivity to taxane-based chemotherapy. In prostate cancer, periprostatic adipose tissue actively secretes IGF-1, which activates IGF-1R signaling and induces switch to the β -tubulin isoform TUBB2B. This specific isoform alters the docetaxel-binding domain, thereby reducing drug affinity and conferring resistance. To counteract this, pharmacologic inhibition of IGF-1R with agents such as AG1024 effectively reverses this resistance in both *in vitro* and *in vivo* models. These findings emphasize that disrupting the IGF-1–TUBB2B axis is a viable approach to dismantle the paracrine protection provided by the adipocytic niche (Liotti *et al.*, 2021).

In obesity-associated TNBC, adipocyte-conditioned media and elevated systemic SERPINE1 promote radioresistance

by enhancing DNA double-strand break repair. This molecular adaptation allows malignant cells to circumvent the lethal effects of ionizing radiation, thereby facilitating tumor survival and progression under therapeutic stress. To address this resistance, recent studies have demonstrated that either genetic knockdown or pharmacological inhibition of SERPINE1, such as with the small-molecule inhibitor tiplaxtinin, effectively impairs these repair pathways and restores radiosensitivity. These findings highlight the SERPINE1 signaling axis as a promising therapeutic target to sensitize TNBC to radiotherapy, particularly within the context of an obesity-primed TME (Su *et al.*, 2023).

Together, these studies demonstrate that adipocyte-derived signals are active participants in therapeutic failure. Targeting these paracrine circuits offers a rational strategy to re-sensitize tumors to therapy. Beyond IL-6, HER3, IGF-1R, and SERPINE1, similar strategies could be extended to leptin or resistin signaling, which remain underexplored but pharmacologically accessible axes within the adipocyte–tumor dialogue.

Targeting Metabolic Energy Coupling

Adipocytes actively supply tumor cells with essential metabolic substrates including free fatty acids, cholesterol intermediates, and NAD⁺ precursors. The continuous provision of

Table 2. Mechanism-based therapeutic strategies targeting adipocyte-cancer crosstalk

Intervention	Agents	Mechanism	Cancer type	Reference
Blockade of IL-6/IL-6R signaling	Tocilizumab (Anti-IL-6R)	Inhibits adipocyte- and myeloid-derived IL-6, normalizes tumor vasculature, reduces hypoxia and immunosuppression, restoring sensitivity to anti-VEGF therapy	Breast cancer (obesity-associated)	Incio <i>et al.</i> , 2018 Bessot <i>et al.</i> , 2025
Dual FGFR and HER3 inhibition	Erdafitinib (FGFR inhibitor), Pertuzumab (HER3 antagonist)	Blocks adipocyte-precursor-derived NRG1 activation of HER3, preventing escape from FGFR inhibition and reversing acquired resistance	FGFR-driven solid tumors (e.g., bladder, others as modelled)	Hosni <i>et al.</i> , 2024
IGF-1R inhibition	AG1024 (IGF-1R inhibitor)	Blocks periprosthetic adipose-derived IGF-1, prevents TUBB2B β -tubulin isoform switch that lowers docetaxel binding, restoring taxane sensitivity	Prostate cancer	Liotti <i>et al.</i> , 2021
SERPINE1 inhibition	Tiplaxitin (SERPINE1 inhibitor)	Inhibits adipocyte-conditioned SERPINE1 signaling that enhances DNA double-strand break repair, resensitizing tumors to radiotherapy	Triple-negative breast cancer (obesity-associated)	Su <i>et al.</i> , 2023
FAO inhibition	Etomoxir (CPT1 inhibitor)	Blocks transfer of fatty acids and FAO enzymes (e.g., CPT1A, HADHA) via adipocyte exosomes, reducing OXPHOS/ATP production and reversing metabolic resistance	Ovarian cancer (Multiple solid tumors in adipocyte-rich niches)	Lazar <i>et al.</i> , 2016
Blockade of exosome biogenesis	GW4869 (nSMase2 inhibitor)	Prevents adipocyte-to-tumor transfer of FAO-supporting lipids and enzymes	Ovarian cancer	Lazar <i>et al.</i> , 2016
PPAR γ pathway inhibition	GW9662 (PPAR γ antagonist)	Inhibits PPAR γ -driven utilization of adipocyte-derived lipids, restoring doxorubicin sensitivity in adipocyte-conditioned cells	Breast cancer	Mentoor <i>et al.</i> , 2021
NAMPT, PARP1 inhibition	FK866 (NAMPT inhibitor), Olaparib (PARP1/2 inhibitor)	Disrupts adipocyte-induced A1BG–NAMPT–PARP1 signaling, impairing DNA repair and reversing cisplatin resistance	Ovarian cancer (Solid tumors with adipocyte-mediated cisplatin resistance)	Liang <i>et al.</i> , 2025
Inflammasome inhibition	Disulfiram (pyroptosis inhibitor)	Prevents adipocyte pyroptosis-mediated release of ATP and FFAs that recruit macrophages and promote inflammatory chemoresistance, thereby restoring chemosensitivity	Ovarian cancer (ovmental fat metastasis)	Lin <i>et al.</i> , 2024
Leptin/ObR inhibition	Leptin receptor antagonist	Blocks adipocyte-derived leptin–LEPR signaling, dampening PI3K/AKT, MEK/ERK and JAK2/STAT3 activation and reducing leptin-driven proliferation and therapy resistance	Prostate cancer	Bessot <i>et al.</i> , 2025
FAO inhibition	BD62694 (FABP4 inhibitor)	Inhibits FABP4-dependent uptake and trafficking of adipocyte-derived free fatty acids, weakening AKT/MAPK survival signaling and adipocyte-supported metastatic chemoresistance	Ovarian cancer, cancer	Bessot <i>et al.</i> , 2025
Anti-inflammatory and metabolic modulation	anti-inflammatory/metabolic drugs (e.g., metformin, NSAIDs, others as applicable)	Suppresses BMA-derived IL-6, leptin, and FFA signaling to mTOR/NF- κ B, attenuating metastasis and therapy resistance in bone marrow adipose niches	Bone marrow-associated malignancies	Bessot <i>et al.</i> , 2025

Table 2 summarizes mechanism-based therapeutic interventions designed to disrupt the metabolic and signaling crosstalk between adipocytes and tumor cells. These strategies aim to reverse adipocyte-mediated drug resistance and enhance the efficacy of conventional anticancer regimens across various adipose-rich cancer types. IL-6, interleukin-6 receptor; VEGF, vascular endothelial growth factor; FGFR, fibroblast growth factor receptor; TUBB2B, tubulin beta 2B class 1b; SERPINE1, serine protease inhibitor family E member 1; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; CPT1A, carnitine palmitoyltransferase 1A; HADHA, hydroxyacyl-CoA dehydrogenase trifunctional effector complex subunit alpha; OXPHOS, oxidative phosphorylation; ATP, adenosine triphosphate; nSMase2, neutral sphingomyelinase 2; PPAR γ , peroxisome proliferator-activated receptor gamma; NAMPT, nicotinamide phosphoribosyltransferase; PARP1, poly(ADP-ribose) polymerase 1; A1BG, alpha-1-B glycoprotein; LEPR/ObR, leptin receptor; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; FABP4, fatty acid binding protein 4; MAPK, mitogen-activated protein kinase; BMA, bone marrow adipocyte; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NSAID, non-steroidal anti-inflammatory drug.

these molecules enables malignant cells to maintain robust oxidative metabolism and sustain survival even under conditions of therapy-induced stress. Based on these mechanistic insights, recent studies have demonstrated that interfering with adipocyte–tumor metabolic coupling effectively restores therapeutic responsiveness. For example, Lazar *et al.* demonstrated that adipocyte-derived exosomes deliver fatty acids and FAO-related enzymes to cancer cells, thereby enhancing OXPHOS and ATP production. Inhibition of FAO (etomoxir) or exosome biogenesis (GW4869) abolished the metabolic support highlighting the crucial role of metabolic energy coupling in adipocyte-mediated therapy resistance. Such findings extend beyond a simple inhibitory observation. They indicate that exosome biogenesis pathways (e.g., nSMase2, Rab27a) and FAO enzymes (e.g., CPT1A, HADHA) may serve as drug-gable metabolic hubs regulating therapeutic resistance (Lazar *et al.*, 2016).

Beyond exosome-mediated lipid delivery, targeting fatty acid trafficking represents an upstream intervention strategy in adipocyte–tumor metabolic coupling. FABP4 mediates the uptake and intracellular transport of adipocyte-derived fatty acids, and its inhibition (e.g., BD62694) disrupts lipid flux, suppresses AKT/MAPK signaling, and weakens adipocyte-supported metastatic chemoresistance (Bessot *et al.*, 2025). Suppression of PPAR γ activity with GW9662 restores doxorubicin sensitivity in TNBC cells exposed to adipocyte-conditioned medium. These results demonstrate that adipocyte–tumor energy coupling is a pharmacologically targetable interaction, and that PPAR γ inhibition represents a practical therapeutic approach to overcoming adipocyte-driven metabolic resistance (Mentoor *et al.*, 2021).

Further, the discovery of the adipocyte-derived NAMPT–PARP1 axis provides a novel metabolic target to bypass DNA repair-mediated resistance. Since adipocyte-secreted A1BG serves as a key ligand that stabilizes NAMPT within cancer cells and thereby fuels the NAD $^{+}$ -dependent PARP1 repair machinery, disrupting this metabolic coupling offers a potent therapeutic window. Specifically, pharmacological inhibition of this axis using the NAMPT inhibitor FK866 or the PARP1 inhibitor olaparib has been shown to effectively deplete the cellular energy required for DNA maintenance and restore the sensitivity of osteosarcoma cells to cisplatin (Liang *et al.*, 2025). This approach suggests that targeting the metabolic fuels provided by the adipose microenvironment can synergize with conventional DNA-damaging agents.

Collectively, these findings highlight metabolic coupling as a therapeutically exploitable vulnerability. Rather than targeting tumor metabolism in isolation, disrupting the metabolic interplay between adipocytes and cancer cells may dismantle an adaptive circuit that drives therapy resistance. Future combinatorial strategies that integrate metabolic inhibitors with cytotoxic or targeted agents could offer an effective approach for treating adipose-rich or obesity-associated malignancies.

Reprogramming of the Inflammatory Microenvironment

Adipocytes shape the immune and inflammatory landscape of tumors, establishing an immunometabolic niche that favors cancer cell survival under therapy-induced stress. Modulation of the inflammasome–pyroptosis axis represents a viable therapeutic strategy to alleviate chemoresistance in adipose-rich tumors. In ovarian cancer, adipocyte pyroptosis within the omental fat actively drives resistance by releasing ATP and

free fatty acids, which recruit macrophages and promote inflammatory signaling. Inhibiting this pathway with the pyroptosis inhibitor disulfiram effectively restores chemosensitivity, underscoring adipocyte death as a critical source of pro-resistance cues in the TME (Lin *et al.*, 2024).

Repositioning existing anti-inflammatory or metabolic modulators holds significant clinical promise for treating therapy-resistant cancers involving BMAs. This therapeutic strategy is supported by the fact that the resulting inflammatory signaling cascades are pharmacologically validated targets across multiple diseases. Specifically, BMAs facilitate metastasis and therapy resistance by secreting various pro-tumor factors, including IL-6, leptin, and free fatty acids (FFAs). These factors activate key signaling pathways, notably mTOR and NF- κ B, which drive the resistance phenotype. Accordingly, leveraging existing agents that target these inflammatory and metabolic axes—such as metabolic modulation by metformin—provides a mechanism-based, and clinically feasible strategy to overcome BMA-mediated therapy resistance (Bessot *et al.*, 2025).

Ultimately, adipocyte-driven inflammation is not a mere by-product of tumor progression but an immunometabolic axis that sustains cancer cell survival under therapeutic stress. Reprogramming this inflammatory circuitry thus emerges as a critical therapeutic direction for overcoming therapy resistance and restoring treatment responsiveness.

TRANSLATIONAL CHALLENGES IN TARGETING ADIPOCYTE–CANCER INTERACTIONS

Despite growing mechanistic evidence indicating that adipocytes contribute to tumor progression and therapy resistance, translating these insights into clinically effective therapeutic strategies remains challenging (Cao, 2019). One major limitation arises from the essential physiological roles of adipose tissue in systemic metabolic regulation. Adipocytes function as central regulators of lipid buffering, glucose metabolism, and endocrine signaling, thereby sustaining whole-body metabolic homeostasis (Bluher, 2013; Kershaw and Flier, 2004). Therefore, systemic inhibition of adipocyte-associated pathways could perturb metabolic homeostasis and provoke systemic complications, including ectopic lipid accumulation, insulin resistance, and endocrine dysregulation (Bluher, 2013).

An additional layer of complexity arises from the intrinsic heterogeneity of adipose tissue. Notably, visceral and subcutaneous adipose depots differ not only in their molecular characteristics, such as inflammatory activity and metabolic function (Lee *et al.*, 2013; Schoettl *et al.*, 2018), but also in the intensity and functional consequences of their interactions with tumor cells. For example, omental adipocytes have been shown to promote lipid transfer to tumor cells and to secrete MCP-1, thereby activating the CCR2–PI3K/AKT/mTOR signaling axis and contributing to cisplatin resistance (Sun *et al.*, 2020), whereas subcutaneous adipose tissue exhibits relatively lower inflammatory signaling and limited lipolytic activity, restricting its capacity to sustain these resistance-promoting pathways (Tchkonina *et al.*, 2013). These depot-specific differences indicate that adipose tissue heterogeneity modulates tumor cell survival under therapeutic stress and ultimately influences treatment efficacy.

Another critical barrier to clinical translation is the reduced effective drug bioavailability within adipocyte-rich niches.

Bone marrow adipocytes have been shown to sequester lipophilic chemotherapeutic agents such as doxorubicin within intracellular lipid droplets, thereby lowering the local drug availability to adjacent tumor cells. This adipocyte-mediated drug sequestration establishes a pharmacological sanctuary in which cancer cells are exposed to sublethal drug concentrations, ultimately promoting therapy resistance (Kwak and Lee, 2023).

These challenges underscore the difficulty of developing universally effective adipocyte-targeted interventions and highlight the need for context-specific strategies that selectively disrupt tumor–adipocyte interactions while preserving the essential systemic functions of adipose tissue.

CONCLUSION & FUTURE PERSPECTIVES

The growing recognition that adipocyte-mediated therapy resistance arises from diverse and multifaceted mechanisms underscores an urgent need to bridge mechanistic discoveries with clinical translation. Future research must primarily address the spatial and contextual heterogeneity of adipose tissues, as adipocytes from distinct depots—such as omental, periprostatic, or bone marrow sites—display unique secretomes and exert context-dependent effects on neighboring tumor cells. Developing advanced *in vivo* models and patient-derived organoids that faithfully recapitulate these site-specific interactions will be critical for identifying predictive biomarkers, such as depot-specific adipokines or exosomal cargos, that can guide patient stratification and therapeutic decision-making.

A critical research priority involves the elucidation of non-canonical mediators that govern the intricate communication between adipocytes and cancer cells. EVs, enriched in regulatory RNAs, lipids, and enzymes, are emerging as potent conveyors of resistance signals, yet their cargo composition, uptake mechanisms, and functional integration within tumor cells remain incompletely understood. Parallel efforts should also explore other unconventional routes of adipocyte influence—including the transfer of mitochondria and other organelles, the sequestration or inactivation of chemotherapeutic agents, and potentially unrecognized modalities such as ECM remodeling, mechanosensitive signaling, and lipid droplet-mediated intercellular transport. Together, these emerging mechanisms highlight that adipocyte–tumor communication extends far beyond classical paracrine signaling, revealing new avenues for intervention that remain largely untapped.

Finally, translating these insights into clinical practice will hinge on integrating adipocyte-targeted interventions with existing anticancer regimens. The mechanistic convergence of adipocyte-driven resistance with pharmacologically validated pathways—such as IGF-1R/PI3K/mTOR and NF- κ B—creates immediate opportunities for drug repositioning and combination strategies. Utilizing clinically available metabolic and anti-inflammatory agents to suppress the adipocyte secretome or its downstream effectors could accelerate bench-to-bedside progress. Ultimately, redefining adipose tissue from a passive stromal component to a dynamic therapeutic target may transform the management of obesity-associated and adipose-rich cancers, converting a metabolic liability into a new avenue for precision oncology.

CONFLICT OF INTEREST

The authors have declared that no competing interest exists.

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