



REVIEW

Etiology and Pathophysiology

Lipids and adipocytes involvement in tumor progression with a focus on obesity and diet

Chiara Calabrese¹ | Giacomo Miserocchi¹  | Alessandro De Vita¹ |
 Chiara Spadazzi¹ | Claudia Cocchi¹  | Silvia Vanni¹ | Sofia Gabellone¹ |
 Giovanni Martinelli² | Nicoletta Ranallo³ | Alberto Bongiovanni³ | Chiara Liverani¹

¹Preclinical and Osteoncology Unit, Biosciences Laboratory, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

²Scientific Directorate, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

³Clinical and Experimental Oncology, Immunotherapy, Rare Cancers and Biological Resource Center, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Correspondence

Giacomo Miserocchi, Preclinical and Osteoncology Unit, Biosciences Laboratory, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Via P. Maroncelli 40, 47014 Meldola, Italy.
 Email: giacomo.miserocchi@irst.emr.it

Funding information

This work was supported by an Italian Ministry of Health Grant for the project GR-2019-12370014.

Summary

The adipose tissue is a complex organ that can play endocrine, metabolic, and immune regulatory roles in cancer. In particular, adipocytes provide metabolic substrates for cancer cell proliferation and produce signaling molecules that can stimulate cell adhesion, migration, invasion, angiogenesis, and inflammation. Cancer cells, in turn, can reprogram adipocytes towards a more inflammatory state, resulting in a vicious cycle that fuels tumor growth and evolution. These mechanisms are enhanced in obesity, which is associated with the risk of developing certain tumors. Diet, an exogenous source of lipids with pro- or anti-inflammatory functions, has also been connected to cancer risk. This review analyzes how adipocytes and lipids are involved in tumor development and progression, focusing on the relationship between obesity and cancer. In addition, we discuss how diets with varying lipid intakes can affect the disease outcomes. Finally, we introduce novel metabolism-targeted treatments and adipocyte-based therapies in oncology.

KEYWORDS

adipocytes, cancer, diet, lipids, obesity

Abbreviations: AA, arachidonic acid; ASC, adipose stromal cell; AT, adipose tissue; ATP, adenosine triphosphate; BMI, body mass index; CAA, cancer-associated adipocyte; CAD, coronary artery disease; CAF, cancer-associated fibroblast; CPT1, carnitine palmitoyltransferase 1; CPT-1, carnitine palmitoyltransferase-1; CR, caloric restriction; CTC, circulating tumor cell; DDS, drug delivery system; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EPA, eicosapentaenoic acid; EV, extracellular vesicle; FA, fatty acid; FAO, fatty acids oxidation; FASN, fatty acid synthase; FFA, free fatty acid; FMD, fasting-mimicking diet; HCC, hepatocellular carcinoma; HFD, high-fat diet; LBCL, large B-cell lymphoma; LCFA, long-chain fatty acid; LD, lipid droplet; LDLR, low-density lipoprotein receptor; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; MUFA, monounsaturated fatty acid; NK, natural killer; NP, nanoparticle; NSCLC, non-small cell lung cancer; OXPHOS, oxidative phosphorylation system; PDX, orthotopic-patient-derived xenograft; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SAT, subcutaneous adipose tissue; SCFA, short-chain fatty acid; SFA, saturated fatty acid; TAG, triacylglycerol; TCA, tricarboxylic acid cycle; TG, triglyceride; TGF, transforming growth factor; TME, tumor microenvironment; TNBC, triple-negative breast cancer; VAT, visceral adipose tissue; WD, Western diet.

1 | INTRODUCTION

The prevalence of obesity has increased worldwide over the last decades.¹ The obesity state refers to an accumulation of excess fat deposits with a body mass index (BMI) over 30 kg/m².² In individuals with obesity, genetic and environmental factors, such as food contaminants, as well as eating habits, play an important role in determining body composition.² Additionally, an imbalance between calorie intake and physical activity results in a chronic positive energy balance, leading to weight gain.³

According to numerous epidemiological studies, obesity is related to an increased risk of developing certain cancers, such as pancreatic,

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *Obesity Reviews* published by John Wiley & Sons Ltd on behalf of World Obesity Federation.

colorectal, postmenopausal breast, ovarian, endometrial, liver, kidney (renal cell), esophagus (adenocarcinoma), gastric, and gallbladder.^{4–6} A high BMI is also linked to a more aggressive disease and adverse outcomes in prostate cancer. This might be linked to the migration of prostate cancer cells towards periprostatic adipose tissue (AT), which provides lipid mediators and inflammatory cytokines in support of cancer cell growth and motility.^{7,8}

However, regardless of global body composition, fat depots can be divided into visceral and subcutaneous, which have different structures and functions in cancer development and progression. Visceral adipose tissue (VAT) has been linked to increased amounts of tumor-promoting metabolites, including free arachidonic acid, phospholipases, prostaglandin synthesis-related enzymes, and lipid metabolites related to inflammation compared to subcutaneous adipose tissue (SAT).⁹ VAT adipocytes are also lipolitically more active than SAT adipocytes and contribute more to plasma-free fatty acid levels, particularly in obese individuals.¹⁰ In patients with colon, esophageal, and renal cancers, VAT has been linked to worse clinical outcomes, which include short- and long-term survival, recurrence, and postoperative.^{9,10} Instead, research exploring the prognostic significance of subcutaneous obesity in cancer patients has produced inconsistent findings. For instance, a high SAT was linked to a higher survival rate in patients with bone metastases and hepatocellular cancer.⁹ Hence, there is growing interest in understanding how adipocytes and AT contribute to tumor development and progression via direct and indirect crosstalk with cancer cells, considering that adipocytes are not always in immediate contact with cancer cells.

In addition, an increasing body of evidence highlighted the role of metabolism in tumors. In particular, dysregulated lipid metabolism is a feature of malignant cells that can exploit cells in the tumor microenvironment (TME) to enhance their use of lipids and boost their proliferation.¹¹ Indeed, cancer cells can increase *de novo* lipogenesis and lipid accumulation, fatty acid (FA) uptake, and FA oxidation (FAO) for energy production.^{12–14} In particular, the presence of cancer-associated adipocytes (CAAs) has been found in the TME of breast and abdominally metastasizing cancers (e.g., gastric, colon, and ovarian).¹⁵

Other distinctive hallmarks of obesity are low-grade inflammation,¹⁶ hormonal alterations,¹⁷ insulin resistance, hypercholesterolemia,¹⁸ and an intensified adipokines secretion.¹⁹ These events can trigger tumorigenesis, cancer progression, and a modified response to therapies^{18,20} by reinforcing tumor-promoting inflammation²¹ and increasing angiogenesis.²²

Finally, diet is the source of exogenous lipids and is linked to several human cancers.²³ Epidemiological, clinical, and laboratory evidence have linked excess calorie consumption with increased cancer risk, while a low-carbohydrate and low-fat diet is associated with reduced cancer incidence.^{24,25} An explanation for this phenomenon could be that dietary alterations may modify circulating concentrations of metabolites, which then influence the composition of the TME, thus driving tumor progression and altering therapeutic responsiveness.²⁶

Our review analyzes how adipocytes contribute to the tumor progression and how lipid metabolism is altered in cancer, with a particular focus on the role of TME. The importance of lipids in cancer will also be analyzed for their function in tumor suppression through ferroptosis, a recently discovered programmed cell death event. We also discuss scientific studies examining the influence of diets with different lipid intakes on disease outcomes. Finally, we analyze the most recent and relevant treatments, which have been developed to target lipid metabolism and adipocyte-based cell therapies in oncology (Figure 1).

2 | TUMOR METABOLISM

2.1 | Overview

Cancer cells have a prevalent mechanism of producing energy, which differs from normal cells. They use aerobic glycolysis to produce adenosine triphosphate (ATP), and most of the generated pyruvate is converted into lactate. This is unlike normal cells, which use the mitochondrial oxidative phosphorylation system (OXPHOS) to produce energy. This change in metabolism is known as the “Warburg effect,” and it occurs even when oxygen is abundant, despite OXPHOS producing a greater number of ATP molecules.²⁷ By providing precursors for numerous metabolic pathways, the Warburg effect could be advantageous to cancer cells.²⁸ Indeed, substrates for the bioenergetic pathways that support tumor growth, such as nucleotide, lipid, and protein synthesis, including glucose, glutamine, lactate, pyruvate, hydroxybutyrate, acetoacetate, acetate, and free fatty acids (FFAs), are increased in production during cancer.^{29,30}

2.2 | Metabolic coupling between cancer and stromal cells in the TME

Recent findings have uncovered an additional intriguing function of the TME in determining the metabolic profile of tumor cells.³¹ The TME consists of extracellular matrix (ECM) proteins and several stromal cell types such as endothelial cells, fibroblasts, immune cells, pre-adipocytes, adipocytes, and inflammatory cells. The TME provides nutrients, growth factors, and other extracellular molecules to tumor cells, affecting their metabolism and boosting their growth.³² Recent evidence suggests that tumor cells may exploit stromal cells to get more metabolic substrates such as glucose, lactate, glutamine, and FAs by stimulating their glycolysis and lipolysis pathways to increase energy production through a “reverse Warburg effect.”³³ According to the hypothesis provided by Martinez-Outschoorn et al.,²⁹ cancer cells cause oxidative stress in nearby stromal cells, which in turn trigger aerobic glycolysis, thus generating extra lactate and/or pyruvate. These high-energy compounds can then be transported to nearby cancer cells, where they enter the tricarboxylic acid cycle (TCA), causing an increase in oxidative phosphorylation and a boost in ATP generation. The metabolic coupling between stromal and cancer cells was

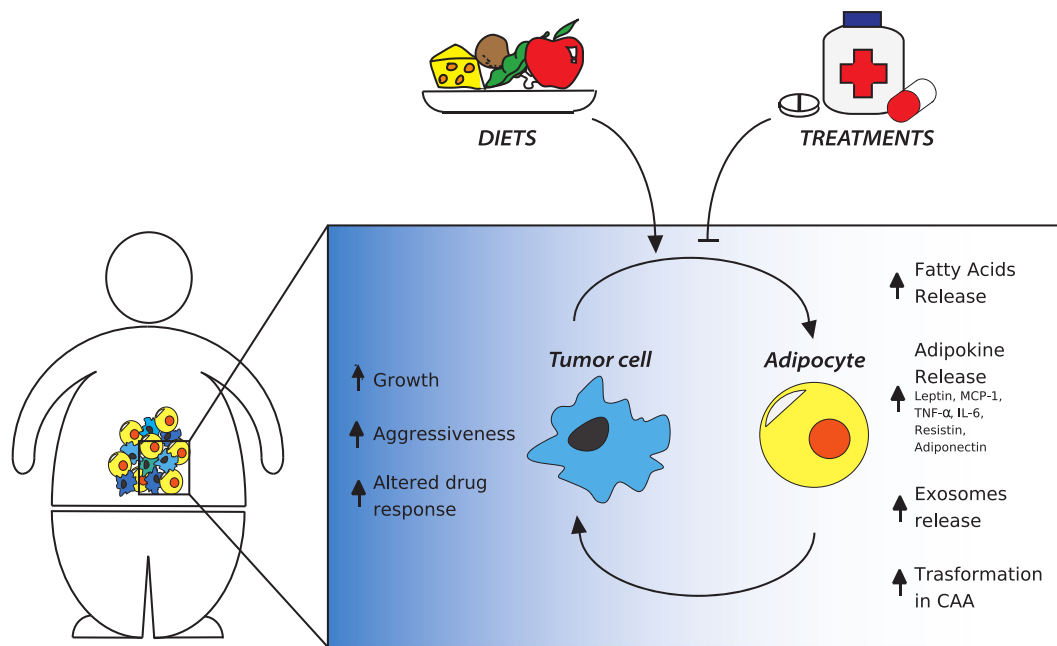


FIGURE 1 Overview of the adipocyte-tumor cell crosstalk. An overview of the main events defining the crosstalk between adipocyte and tumor cell. The latter induces adipocyte transformation into cancer-associated adipocyte (CAA). In addition, cancer cell boosts the release of fatty acids, adipokines (including leptin, MCP-1, resistin, TNF- α , adiponectin, and IL-6), and exosomes from adipocytes. These signaling molecules, in turn, promote cancer cell growth and aggressiveness and alter cell drug response. Pharmacological treatments inhibiting this vicious cycle are under development, and the involvement of different diets is being studied.

demonstrated in experimental models of breast, ovarian, prostate, and sarcomas.²⁹ This relationship has also been observed in several human tumors, such as prostate,³⁴ lung,³⁵ breast, pancreatic, and gastric cancers.³⁶

The reorganization of metabolic pathways is now recognized as a distinctive feature of malignant cells. It is becoming more and more attractive because of its implication as a potential therapeutic target.³⁷ Currently, several ongoing studies are exploring the development of anticancer treatments that target lactate,³⁸ pyruvate,³⁹ acetyl CoA,⁴⁰ FAs (discussed in detail in this review),⁴¹ and amino acids metabolism.⁴²

2.3 | Dysregulated lipid metabolism in support of tumor growth and metastasis

An explanation for the metabolic shift in cancer cells during tumor development is the activation of specific pathways that supply metabolic substrates to support their growth and proliferation. Lipids are among the most important cellular elements whose production increases during cancer progression.³⁹ They are hydrophobic molecules which include sterols, monoglycerides, diacylglycerides, triglycerides (TGs), phospholipids, and glycolipids. The major components of lipids are FAs, a group of molecules consisting of hydrocarbon chains varying in length and saturation.

One of the major functions of lipids is their contribution to composing biological membranes in the form of phospholipids, which are

amphipathic molecules.⁴³ Lipids can also act as mediators or signaling molecules.⁴⁴ The most coherent example consists of polyunsaturated fatty acids (PUFAs), which include arachidonic acid (AA), an omega-6-derived PUFA, and the substrate for the synthesis of eicosanoids, such as prostaglandins, thromboxanes, and leukotrienes. These play a role in tissue inflammation and promote a pro-tumorigenic environment.^{21,45} Other PUFAs with signaling functions are the omega-3 FAs (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), which are believed to reduce inflammatory processes and the risk of breast and other cancers.⁴⁶ As previously mentioned, tumor cells can promote lipolysis in adjacent adipocytes.¹¹ Accordingly, a metabolic symbiosis takes place between these cells and leads to the storage and mitochondrial use of adipocyte-derived FAs by cancer cells.⁴⁷ Bochet et al.⁴⁸ demonstrated that, after co-culture with tumor cells, lipid content is released from tumor-surrounding adipocytes and the FAs are transferred to cancer cells. The movement of lipids has been proven in both prostate⁴⁹ and ovarian cancers.⁵⁰ Various studies showed how breast cancer cells exposed to adipocyte-conditioned media, or in co-culture with adipocytes, modified proliferation, migration, and invasion.^{51,52} Analogous results have been noticed in 3D cultures⁵³ and xenograft models.⁵⁴ In particular, Nieman et al.⁵⁰ proved that primary human omental adipocytes promote gastric, breast, colon, and ovarian cancer cell proliferation and metastasis in vitro and ovarian cancer growth in vivo. They demonstrated that adipocytes facilitate the early homing of ovarian tumor cells to the omentum by producing adipokines. Then, lipid transfer from adipocytes to cancer cells accelerates the growth of metastases. This process may not be specific to

ovarian cancer cells and explains the proliferation of other cancerous cell types that migrate to the abdomen or areas with a high concentration of adipocytes.

Lipid metabolism can also be affected by variable oxygen tension and hypoxia in the TME. Tumor cells exposed to hypoxia enhance FA uptake⁵⁵ and the expression of lipid uptake-associated proteins. In particular, CD36 (a fatty acid transport protein) in the lung, bladder, breast, and ovarian cancers^{56,57} and the low-density lipoprotein receptor (LDLR) in pancreatic cancer are associated with unfavorable prognosis in patients.⁵⁸ Moreover, adverse environmental conditions, such as high acidity⁵⁹ or glucose deprivation,⁶⁰ can stimulate the upregulation of FAO, which many tumors rely on for their survival. This has been observed in lung,⁶¹ ovarian,⁵⁰ colorectal,⁶¹ and breast⁶² cancers. Overexpression of FAO enzymes has been observed in these types of cancer,⁶³ and arresting FAO slows down tumor growth in several experimental models. Specifically, inhibiting carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme in FAO, was demonstrated to hinder tumor progression and prolong survival in an orthotopic-patient-derived xenograft (PDX) triple-negative breast cancer (TNBC) model,⁶² in a PDX model of glioblastoma,⁶⁴ and in an animal model of liver cancer.⁶⁵

In an interesting research by Li et al.,⁶⁶ they examined the role of obesity in metabolic alterations occurring in myeloma patients. By analyzing circulating tumor cells (CTCs) isolated from patients affected by obesity, the authors recognized the involvement of the acetyl coenzyme A (acetyl-CoA) metabolic pathway in myeloma growth. Acetyl-CoA, a key metabolite acting as an essential intermediate for pyruvate to take part in the TCA cycle, is the main precursor of **lipid synthesis**.⁶⁷ The limiting enzyme for acetyl-CoA production from acetate is acetyl-CoA synthetase 2 (ACSS2). In metabolic stressful conditions, such as hypoxia and glucose deprivation, ACSS2 can promote cancer progression by acetyl-CoA production.^{68,69} Li et al.⁶⁶ demonstrated that in myeloma patients, the expression of ACSS2 was positively correlated with BMI values. Comparing patients with normal weights (BMI < 25 kg/m²) and patients affected by obesity (BMI > 30 kg/m²), the authors identified many genes involved in pathways related to inflammatory response and metabolic processes, which were differentially expressed in the two groups. Patients with high expression of ACSS2 showed poor overall and relapse-free survival. In general, the patients with BMIs over 30 kg/m² and high expression of ACSS2 had worse prognosis.⁶⁶

3 | ADIPOCYTES PROMOTE TUMOR PROGRESSION THROUGH LOCAL AND SYSTEMIC MECHANISMS

3.1 | Function and endocrine role of adipocytes

Adipocytes play a key role in both growth and metastasis of a number of tumors, including those located in the breast, prostate, ovary, stomach, kidney, and colon.⁸ These cells are among the constituents of AT, and their hallmark is the ability to store excess calories in the form of

triacylglycerols (TAGs) or TGs, which are packaged into large lipid droplets (LDs) and mobilized as needed.^{70,71} When energy demand increases, TAGs undergo the process of lipolysis through which they split into their components: FAs and glycerol. Once released, FAs can participate in different pathways, including β -oxidation (or FAO), which generates energy in the form of ATP, re-esterification into TAGs,⁷² and can act as signaling molecules.⁷³

Adipocytes are also integrated into the systemic metabolism and have a second role as endocrine cells. When the state of positive energy balance is chronic, such as during obesity, the AT changes in adipocyte size, distribution, cellular composition, and function.⁷⁴ In particular, hypertrophic adipocytes, ectopic fat deposition (such as in the liver or heart), hypoxia, and chronic stress occur, subsequently causing a greater secretion of pro-inflammatory adipokines, which are defined as lipid or protein factors (hormones, cytokines, growth factors, and matrix remodeling components) with endocrine and paracrine functions⁷⁵ (Figure 2). These include monocyte chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)- α , interleukin (IL)-6, resistin, adiponectin, and leptin.⁷⁶ Intensified release of these inflammatory mediators induces the chemotaxis of lymphocytes, macrophages, and stromal cells⁷⁷ towards AT, and this results in low-grade chronic inflammation, a typical feature of obesity, which supports cancer progression.^{16,78} For example, TNF- α , IL-6, and MCP-1 are released from adipocytes or from inflammatory cells in AT to stimulate cell proliferation, angiogenesis, and tumor progression.^{74,79} Furthermore, these mediators produce reactive oxygen species (ROS) which have mitogenic properties and have been proposed as tumor promoters.⁸⁰

3.2 | Inflammatory adipokines and cytokines in cancer promotion

As reported above, obesity is correlated with a chronic low-grade state of inflammation that is the effect of a heightened concentration of FAs, inflammatory cytokines, immune cells such as macrophages and also adipokines released by adipocytes⁸¹ (Table 1).

One of the well-known adipokines is leptin, which is produced by local and distant adipocytes and by other cells within the TME and acts in endocrine, paracrine, and autocrine ways.¹²¹ Leptin blood levels are directly proportional to body fat mass,¹²² being overproduced in individuals with obesity. Clinical and experimental studies have proved the role of leptin in supporting tumor development and progression and in decreasing the efficacy of cancer treatments.⁸² Leptin also has angiogenic properties which may contribute to promoting cancer progression.⁸³ As shown in breast carcinogenesis, leptin signaling regulates a significant number of molecules involved in proliferation, adhesion, migration, invasion, angiogenesis, and inflammation. This occurs through the regulation of the expression of cyclin D1, p53, survivin, IL1, E-cadherin, vascular endothelial growth factor (VEGF), and its receptor type 2, as well as several tissue factors.^{84,85} Leptin promotes pro-survival pathways in cancer cells, for example, **Janus kinase (JAK)**-signal

FIGURE 2 Different adipocyte behavior in lean and obese bodies. In a lean body, adipocytes store excess calories and act as endocrine cells, secreting hormones and signaling molecules. They undergo physiological lipolysis to contribute to energy production when needed. However, in obesity condition, adipocytes become hypertrophic and have an ectopic distribution, accumulating in the liver and heart. This causes chronic stress with secretion of pro-inflammatory adipokines by adipocytes. Adipokines lead to chemotaxis of immune cells and chronic inflammation, the main feature of an obese AT.

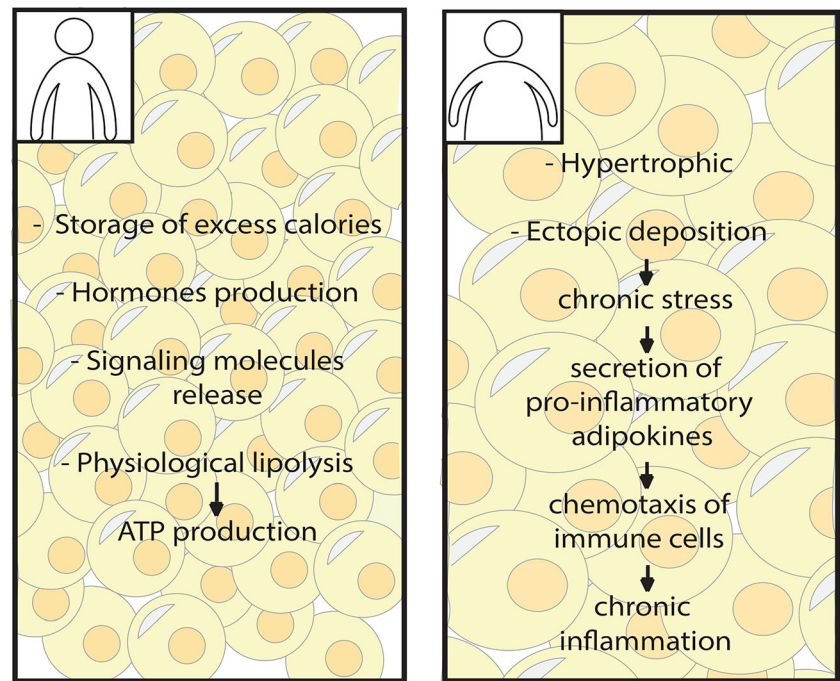


TABLE 1 Adipokines and their effects on cancer.

Adipokines	Effects on tumor	Affected cancer types	Mechanisms	References
Leptin	(↑) tumor development, angiogenesis and progression (↓) efficacy of anticancer drugs	Breast	(↑) cyclin D1, p53, survivin, IL1, E-cadherin, VEGF and its receptor type 2 expression (↑) JAK-STAT3, Akt, JNK, MAPK/ERK1/2, PI3K/AKT-1 Pathways	82–88
Resistin	(↑) risk (↑) metastasis	Gastric, colorectal, liver, pancreatic, ovarian, breast, lung	(↑) EMT via the NF-κB/STAT3 pathway (↑) VEGF production and Akt phosphorylation	89–98
Adiponectin	(↓) risk	Breast, prostate, gastrointestinal, endometrial, hepatocellular	(↓) mTOR phosphorylation (↓) production of pro-inflammatory cytokines by inhibiting NF-κB activity (↑) apoptosis	81, 99–103
IL-6	(↑) tumor growth, angiogenesis, progression	Esophageal, gastric, colorectal, pancreatic, bladder, breast, ovarian, prostate, hepatocellular, renal cell	(↑) JAK-STAT3, SH2-SHP-2-Ras-Raf-MEK-ERK and PI3K-Akt pathways	104–106
TNF-α	(↑) tumor growth, angiogenesis, progression	Lung, pancreatic, breast, prostate	(↑) NF-κB and JNK pathways	104, 107, 108
MCP-1	(↑) migration, angiogenesis, tumor development	Colorectal, breast, lung, hepatocellular, pancreatic, renal, nasopharyngeal	(↑) recruitment of immune cells (↑) PI3K/AKT, MAPK/p38 and JAK/STAT3 pathways	109–120

Note: The table lists the known adipokines, their effects on different types of tumor and mechanisms of action. (↑): increase; (↓): decrease.

transducer and activator of transcription 3 (STAT3), Akt, and c-Jun N-terminal kinase (JNK) by binding to its receptor ObR.⁸⁶ Transcription of genes that regulate cellular proliferation and invasiveness, such as telomerase reverse transcriptase, IL-6, transforming growth factor (TGF), matrix metalloproteinases (MMP)9, and MMP13, is induced by the activation of these signaling pathways.⁸⁷ Moreover, this adipokine cooperates with different oncogenes, cytokines, and

growth factors such as JAK/STAT3, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)1/2, and phosphoinositide 3-kinase (PI3K)/AKT-1.⁸⁸ It is interesting to note that leptin signaling also influences metabolic remodeling in cancer cells: in the absence of leptin receptors, mammary cancer cells exhibit increased mitochondrial oxidation and decreased glycolysis.¹²³

Resistin, like leptin, is a type of adipokine that increases the risk of developing a variety of tumors such as gastric,⁸⁹ colorectal,⁹⁰ liver,⁹¹ pancreatic,⁹² ovarian,⁹³ breast,⁹⁴ and lung cancer.⁹⁵ Resistin mainly promotes epithelial-mesenchymal transition (EMT), a process during which individual cells enhance their motility and acquire an invasive phenotype as a result of loss of epithelial cell junctions, reorganization of their cytoskeleton, and reprogramming of gene expression, events that promote cancer progression.⁹⁶ Resistin stimulates EMT via the nuclear factor- κ B (NF- κ B)/STAT3 signaling pathway, VEGF production, and Akt phosphorylation,⁹⁷ thus stimulating metastasis.⁹⁸

Adiponectin is an adipokine that is conversely related to body fat mass and it has anticancer effects. Numerous pieces of evidence proved this inverse relationship between adiponectin blood level and cancer risk in breast,⁹⁹ prostate,¹⁰⁰ gastrointestinal,¹⁰¹ endometrial¹⁰² cancers, and hepatocellular carcinoma.¹⁰³ Adiponectin reduces the mammalian target of rapamycin (mTOR) phosphorylation, which in turn limits the production of pro-inflammatory cytokines by inhibiting NF- κ B activity and induces apoptosis.^{81,103}

Similarly, adipocytes produce the cytokines IL-6 and TNF- α that play a key role in inflammation and immunity. Besides, there is increasing evidence that the AT of individuals with obesity has a great infiltration of macrophages that are stimulated by adipocytes to switch from the M2 phenotype to M1. This causes a shift from anti-inflammatory cytokines produced by M2 macrophages, such as IL-10, to pro-inflammatory cytokines such as IL-6 and TNF- α produced by M1 macrophages.¹²⁴ Therefore, both the production and secretion of these two cytokines rise in individuals with obesity and enhance tumorigenesis via their pro-inflammatory effects. IL-6 and TNF- α intensify tumor proliferation, survival, and angiogenesis driving carcinogenesis and cancer progression.¹⁰⁴ TNF- α acts as a tumor promoter also activating the NF- κ B and JNK signaling pathways.¹⁰⁷ High levels of circulating TNF- α were found in patients with lung, pancreatic, breast, and prostate cancers.¹⁰⁸ Likewise, serum IL-6 had been reported to be associated with poor prognosis in oesophageal, gastric, colorectal, pancreatic, bladder, breast, ovarian, prostate, hepatocellular, and renal cell carcinomas.¹⁰⁵ This inflammatory factor can activate the JAK-STAT3 pathway, the Src homology 2 (SH2)-containing protein tyrosine phosphatase-2 (SHP-2)-Ras-Raf-mitogen-activated protein kinase (MEK)-ERK pathway and the PI3K-Akt pathway, therefore taking part in differentiation, proliferation, migration, and apoptosis of cancer cells.¹⁰⁶

MCP-1, also known as chemokine (C-C motif) ligand 2 (CCL2), is another inflammatory factor secreted by adipocytes. The binding between CCL2 and its receptor CCR2 activates a transduction pathway that leads to the recruitment of immune cells, especially monocytes, memory T lymphocytes, and natural killer (NK) cells towards the inflammatory region, playing critical roles in the immune response.¹¹⁰ Other signaling pathways activated by CCL2 are PI3K/AKT, MAPK/p38, and JAK/STAT3 which play a vital role in anti-apoptosis, and cell migration, leading to oncogenic advancement.¹¹¹⁻¹¹³ Also, the expression of CCL2 was significantly associated with neo-angiogenesis.¹¹⁴ It has been demonstrated that the CCL2-CCR2 signaling axis

participated in the development of different types of cancer, such as colorectal,¹¹⁵ breast,¹⁰⁹ lung,¹¹⁶ hepatocellular,¹¹⁷ pancreatic,¹¹⁸ and renal cancers¹¹⁹ and nasopharyngeal carcinoma.¹²⁰

Even though adipokines may independently affect the development of various obesity-related cancers, they could also act together through the crosstalk of their respective downstream signaling pathways. The link between leptin and some cancers often involves adiponectin as well. In esophageal cancer, for example, leptin-induced proliferation of tumor cells could be arrested by adiponectin through AdipoR1 activation.¹⁰¹ Likewise, leptin-induced proliferation of hepatocellular tumor cells can be inhibited by adiponectin via the STAT3 signaling pathway.⁷⁴

3.3 | Cancer-associated adipocytes

Dirat et al.⁵¹ emphasized the crucial role of the peritumoral AT in the progression of breast cancer and were the first to hypothesize that tumor cells may rewire adipocytes in their adjacent microenvironment to assume pro-inflammatory and aggressive phenotypes.¹²⁵ These peritumoral adipocytes were named cancer-associated adipocytes (CAAs). Notably, they discovered that adipocytes co-cultivated with breast cancer cells exhibit peculiar features.^{51,126} CAAs displayed a reduction in size because of the transfer of lipids to cancer cells and an activated phenotype through the downregulation of adipocyte markers like resistin, adiponectin, and fatty acid binding protein (FABP4). Besides, they overproduce adipose-derived factors via endocrine and paracrine signaling pathways, including CCL2, CCL5, IL-6, TNF, VEGF, and leptin.^{51,127} CAAs also generate fibroblast-like cells known as adipocyte-derived fibroblasts when there are cancer cells present, especially at the tumor-invasive front. These cells may represent a subpopulation of cancer-associated fibroblasts (CAFs), and, like them, they are engaged in the malignant evolution of tumors.⁴⁸ Accordingly, Zhu et al.¹²⁸ found that during tumor growth, adipocytes from tumor-invasive mammary fat de-differentiate into fibroblasts-like progenitor cells and fully integrate into the TME, resulting in an adipocyte mesenchymal transition (AMT). The de-differentiated adipocytes change into a variety of cell types related to ECM remodeling, inflammation, and immune response. Although the de-differentiated cells have different metabolisms from CAFs, they have similar impacts on the proliferation of tumor cells. Moreover, this de-differentiation has also been found in histological studies of abdominally metastasizing cancers (ovarian, renal, pancreatic, gastric, and colon).¹²⁸

As reported by Attané and Muller,¹⁴ CAAs undergo multiple catabolic processes resulting in the release of metabolites, such as lactate, pyruvate, FFAs, and ketone bodies. Additionally, a study by Dirat et al.⁵¹ demonstrated that CAAs stimulate the invasive capacities of murine and human breast cancer cell lines. They noticed that when they cultivated tumor cells in a medium conditioned by adipocytes, which have never been co-cultivated with tumor cells, there was no significant increase in the cells' invasive abilities for any of the cell lines. However, when the conditioned medium was derived from

adipocytes previously co-cultivated with tumor cells, significant stimulation of tumor invasive capacities was observed in all the tested models compared with cells grown in the control medium. The results highlighted that a cross-talk between the two cell populations is necessary to obtain this effect. The tumor cell-derived signaling molecules induce lipolysis of adipocytes and promote the evolution of adipocytes to CAAs.⁷¹ This CAA-activated phenotype has been confirmed in vitro in several tumor histotypes (prostate, lung, ovarian, breast¹²⁹ and pancreatic cancers,¹³⁰ melanoma,¹³¹ hepatocarcinoma,¹³² and leukemia¹²⁹) and in vivo at the invasive front of human breast cancer.^{51,133}

Besides CAAs, AT provides progenitor cells that may explain the mechanisms involved in the relationship between obesity and cancer progression. These cells, known as adipose stromal cells (ASCs), are a component of the stromal vascular fraction of AT and are found in greater amounts in individuals with obesity.¹³⁴ They exhibit multipotency and proliferative capacity similar to bone marrow mesenchymal stem cells (MSCs), but they also represent a source of CAFs.¹³⁵ It has been suggested that the recruitment of ASCs by tumor is enhanced in individuals with obesity and that ASCs promote tumor vascularization, proliferation of malignant cells, and resistance to anticancer therapies.^{136,137}

3.4 | Adipocytes-derived exosomes

Recent studies suggest that adipocyte-produced extracellular vesicles (EVs) play crucial roles in obesity and related conditions.¹³⁸ Exosomes are a type of membrane-encapsulated EVs that range in size from 30 to 100 nm. They are released into the extracellular microenvironment by a variety of cell types, including adipocytes and cancer cells, and are transported by different body fluids.¹³⁹ The exchange of the exosome content, which consists of messenger RNAs (mRNAs), long non-coding RNAs (lncRNAs), microRNAs (miRNAs), transcription factors, proteins, and lipids,^{140,141} mediates cell-to-cell biological communication and, in particular, the metabolic symbiosis between adipocytes and various types of cancer cells.¹⁴²

According to a study by Clement et al.,¹⁴³ adipocytes generate large amounts of exosomes that are intended to convey proteins essential in lipid metabolism, including FAO enzymes. These exosomes may play a role in tumor progression that spreads far from AT, such as the early stages of melanoma. The authors demonstrated that the quantity of adipocyte-derived exosomes released by adipocytes¹⁴⁴ and their cargo¹⁴⁵ are influenced by obesity or high-fat dietary interventions. Recent findings show that adipocyte-derived exosomes from patients affected by obesity are more abundant in proteins that facilitate cancer cell invasion and migration by raising FAO.^{142,146} Taken together, these observations indicate that cancer patients with an obesity condition would likely benefit from FAO inhibitors and/or compounds that prevent EV uptake.

Moreover, a review by Bandini et al.¹⁴⁷ discusses how miRNAs secreted by adipocytes are involved in breast cancer progression. They reported a study that demonstrated that miR-144 and miR-126

are carried at a high level by exosomes released after tumor cell-adipocyte interaction and that these miRNAs are responsible for the reprogramming of energy metabolism to facilitate tumor progression.¹⁴⁸

Finally, Wang et al.¹⁴⁹ demonstrated that exosomes from hepatocarcinoma cells may be actively integrated by adipocytes to transform them into tumor-promoting cells (exo-adipocytes). These were then proven to boost tumor development and promote angiogenesis in vivo. According to these findings, there is a complex crosstalk between adipocytes and cancer cells mediated by EVs through which cancer cells can alter AT to create a microenvironment that is favorable to tumor growth.¹⁴⁹

3.5 | Lipid peroxidation is essential for ferroptosis-mediated tumor suppression

Ferroptosis is a recently discovered sort of cell death implicated in various medical conditions and also in different types of cancer, such as large B-cell lymphoma (LBCL), renal cell carcinoma, liver cancer, cervical carcinoma, osteosarcoma, and prostate adenocarcinoma.¹⁵⁰ Ferroptosis is a programmed necrosis, iron dependent, and ROS dependent, whose specific features clearly distinguish it from the other forms of cell death.¹⁵¹ It is primarily characterized by cytological changes, such as diminished or absent mitochondrial crests and destruction of the external mitochondrial membrane.¹⁵¹ Plasma membrane loss of selective permeability is triggered by cell abnormalities caused by massive lipid peroxidation that might be because of ROS accumulation.^{152,153} The main driving factor behind ROS formation is the excessive presence of iron, which originated from abnormal iron metabolism.¹⁵⁴ ROS play a variety of roles in cancer, including promotion of cell growth and survival, DNA damage, genetic instability, cell death induction, and increase of treatment resistance.¹⁵⁵ To decrease ROS levels and keep redox equilibrium, tumor cells express significant quantities of antioxidant proteins. When this redox equilibrium is irreversibly disrupted, cancer cell death happens¹⁵³ (Figure 3). As a result, ferroptosis is progressively recognized as an adaptive ability to eradicate cancerous cells. By eliminating cells that are lacking in essential nutrients or that are damaged by infection or environmental stress, ferroptosis plays a crucial role in the reduction of carcinogenesis.¹⁵⁶

Because PUFAs are easily damaged by ROS, boosting their incorporation into membrane phospholipids is crucial to increase cancer cell susceptibility to ferroptosis. Lipid-peroxyl radicals produced in turn oxidize nearby PUFAs, triggering a chain reaction that, if without restraint, results in cell death.¹⁵² Magtanong et al.¹⁵⁷ revealed that exogenous monounsaturated fatty acids (MUFAs) prevent ferroptosis by displacing PUFAs from membrane phospholipids. Considering these findings, it can be assumed that FA desaturation is closely related to processes that drive programmed cell death. Accordingly, cancer cells need to maintain the correct FA desaturation state to survive.¹⁵⁸

Hence, lipid metabolism significantly affects the cells' sensitivity to ferroptosis. Evidence in breast cancer, fibrosarcoma, and prostate

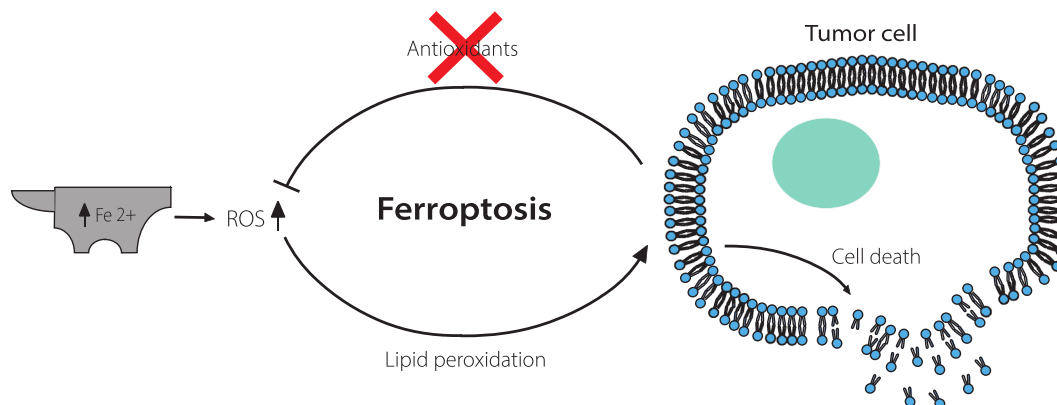


FIGURE 3 The mechanism of ferroptosis. Ferroptosis is a type of cell death, triggered by an excessive presence of iron, which leads to ROS accumulation. This, in turn, causes lipids peroxidation of the tumor cell membrane. The ultimate event is cell death, because of the insufficient production of antioxidants in tumor cells not able to counteract ROS increase.

cancer cells supports the idea that cancer cells may protect themselves by simply depleting membrane PUFAs, given the high demand for PUFA–phospholipids in ferroptosis.^{157,159,160} To enable the reduction of the amount of PUFA-derived ROS in membranes and increase their resistance to lipid peroxidation, cancer cells promote de novo lipogenesis to produce more saturated FAs (SFAs) and MUFAs.¹³

Further research revealed that the molecule erastin could induce ferroptosis and, consequently, the death of cancer cells. Erastin prevents cancer cells from the uptake of cystine, weakening their antioxidant defenses and ultimately causing their death by ferroptosis.¹⁵³ In addition, the combination of the ferroptosis-inducer erastin with chemotherapeutic treatments, such as cytarabine, cisplatin, doxorubicin, and temozolomide, resulted in a notable synergistic antitumor effect.¹⁵⁴

Additionally, ferroptosis can attract and activate immune cells to the tumor sites by releasing chemoattractant molecules. This increases the chance that a ferroptosis-inducer could serve as a suitable enhancer for antitumor immunotherapy treatments like checkpoint inhibitors.¹⁶¹ Nevertheless, a study by Zhang et al.¹⁶² showed that a high body fat ratio was linked to cancer progression and a poor prognosis, partly because of a reduction in ferroptosis. They demonstrated that exosomes secreted by AT inhibit lipid ROS production, thus decreasing ferroptosis susceptibility and promoting chemotherapy resistance in colorectal carcinoma cells.

4 | DIET AS A SOURCE OF EXOGENOUS LIPIDS

4.1 | Pro- and anti-inflammatory dietary fatty acids

In cancer cells, lipids and FAs can be produced either by endogenous lipid synthesis, thanks to the mobilization of collected fat from adipocytes, or exogenously through diet. Some essential FAs, such as PUFAs, are not synthesized by the body and must be obtained through diet.¹⁶³ A study by Hopperton et al.¹⁶⁴ displayed that both

exogenous and endogenous FAs are esterified to the same lipid and phospholipid classes and in the same proportions, suggesting that they are likewise important in stimulating cancer pathogenicity.

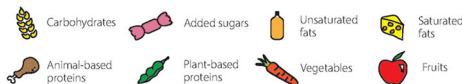
Previous studies have acknowledged diet and nutrition as partly responsible for cancer risk.¹⁶⁵ Epidemiological, preclinical, and clinical research have related obesity and excess calorie consumption with heightened chances of tumor occurrence, while a low-carbohydrate, low-fat diet is linked to lower cancer incidence.^{24,166} Numerous evidences indicated a direct link between high dietary fat intake and the risk of developing colorectal, liver, breast, pancreatic, gastrointestinal, and prostate cancers.¹⁶⁷ This connection might result from a combination of increased consumption of some FAs that support cancer growth and/or decreased intake of other FAs that act as preventives for cancer progression.¹⁶⁸ Indeed, FAs can have pro- or anti-inflammatory effects.^{169,170} Saturated short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, are produced mainly by microbial fermentation of plant-based fibers and have anti-inflammatory properties.¹⁷¹ These lead to cell cycle arrest and cause antiproliferative and proapoptotic effects in cancer cells, in particular in colon cancer.¹⁷²

Another class of FAs are medium-chain fatty acids (MCFAs), which are contained in coconut oil and palm kernels and must be assembled into chylomicrons to be transported towards the liver, unlike the other FAs. The most common MCFAs include capric acid (C:10), lauric acid (C:12), capric acid (C:6), and caprylic acid (C:8). Similar to SCFAs, these MCFAs have been found to possess anticancer properties in in vitro experiments conducted on human breast tissue, skin, and colorectal cancer cells.¹⁷³

However, saturated long-chain FAs (LCFAs), found in dairy fat, coconut oil, palm kernel oil, peanut oil, and meat lipids, have generally been linked to inflammatory effects and tumorigenesis, especially palmitic acid and stearic acid.¹⁷⁴ While SCFAs and MCFAs can passively permeate the cell membrane, LCFAs need a fatty acid translocase, or CD36, for their uptake.¹⁷⁵ In addition to this, a study by Daquinag et al.¹⁷⁶ suggested that CD36 is also involved in LCFAs mobilization from AT, thus stimulating tumor growth and facilitating resistance to

TABLE 2 Diets and their known effects on tumor risk and metabolism.

Diets	Foods composition	Metabolic effects	Effects on tumor	Affected cancer types	References
Caloric restriction		↓ Blood Glucose Level ↓ Lipid Levels ↓ Insulin Levels	↓ Tumor Growth	Breast, lung, prostate, brain, pancreatic, colorectal	191–197
Ketogenic diet		↓ Blood Glucose Level ↓ Inflammation	↑ Efficacy of Anticancer Drugs	Neuroblastoma, glioma, breast, lung, prostate, pancreatic, bladder, endometrial, glioblastoma, colorectal	198, 199
Plant-based diet		No evidence available	↑ Overall Survival	Pancreatic	197
High-fat diet		No evidence available	↑ Tumor Growth ↑ Tumor Incidence	Prostate, hepatocellular, pancreatic, colorectal	200–203
Western diet		↑ Oxidative Stress ↑ Lipid Deregulation ↑ Insulin Resistance	↑ Tumor Incidence	Colorectal	204, 205
Mediterranean diet		↓ Inflammation ↑ Vascular Function ↑ Insulin Sensitivity	↓ Tumor Incidence (when supplemented with extra-virgin oil)	Breast	207, 208
Vegan diet		↓ Obesity ↓ Blood Glucose Levels	↓ Tumor Incidence	Prostate (vegan diet), Gastrointestinal (vegetarian diet)	209
Vegetarian diet					
Fasting-mimicking diet		↓ Blood Glucose Levels ↑ Adiponectin ↓ Leptin	↑ Efficacy of Anticancer Drugs ↑ Anticancer Immunosurveillance	Neuroblastoma, breast, lung, pancreatic, melanoma, fibrosarcoma, mesothelioma, glioblastoma, colorectal	211, 212



Note: The table shows the food composition of the most popular diets, their known metabolic effects, their influence on tumor, and the affected cancer types. Double symbol: the food is highly consumed in the diet analyzed; crossed out symbol: the food is not consumed in the diet analyzed; (↑): increase; (↓) decrease.

chemotherapy. CD36 is expressed in both adipocytes and endothelial cells, which are constituents of vessels in AT, and to a much lesser extent on the cancer cell surface. This led the authors to assume that the key mediator of LCFAs transfer from AT to tumors is exactly CD36 in the endothelium and adipocytes.¹⁷⁶

Moreover, van Dijk et al.¹⁷⁷ discovered a connection among AT inflammation, the presence of SFAs, and the absence of MUFAs. This is in line with a study that demonstrated that the expression of inflammatory genes in AT was enhanced by an SFA-rich diet, while it decreased during a MUFA-rich diet.¹⁷⁸

Concerning the unsaturated FAs, docosahexaenoic (DHA) and eicosapentaenoic (EPA) acids, both ω -3 PUFAs which can be found in fish and other seafood, have anti-inflammatory actions and assist in repairing the damages of inflammation. They are related to a lower incidence of prostate,¹⁷⁹ colorectal,¹⁸⁰ and lung cancers.¹⁸¹ Conversely, arachidonic acid (AA), an ω -6 PUFA that can be found mainly in the fatty parts of meats and fish, is a precursor of eicosanoids that cause inflammation¹⁸² and is directly linked to a higher risk of colorectal cancer in both sexes.¹⁸³ It has been shown that the rise of cancer risk, especially for breast, prostate,^{184,185} and oral cancers, may also be linked with variations in the dietary ω -6/ ω -3 ratio.¹⁸⁶

Exploring this important issue in patients is challenging given that a diet consists of many different foods.²³ By examining the whole nutritional intake, researchers can understand the interplay between various foods, along with the influence on tumor risk of dietary elements associated with each other.¹⁸⁷ However, the authors of the Lien et al. study²⁶ found the deciphering of dietary data challenging because of the variability of the effects that a particular diet exerts on

certain tumors. Considering these challenges, animal models have been used to unravel mechanisms and processes linking diets with specific tumor features. For example, mass spectrometry can be applied to understand how the tumor metabolomic profile is altered in animal models fed with a particular diet.²⁶ Dietary components can impact the growth of tumors by altering cancer cell metabolism through modifications in the access to and use of nutrients by cancer cells. Alterations of diet composition lead to shifts in plasma metabolite levels, which in turn influence metabolite levels in the TME and eventually modify cancer cell metabolism and response to therapy.¹⁸⁸

4.2 | Diet implication in cancer growth and development

Many studies have been published on this topic. In particular, low-carbohydrate diets have been thought to inhibit the growth of several types of cancers¹⁸⁹ (Table 2). Among these are caloric restriction (CR), which consists of chronic reduction by 30–40% of total **calorie intake** typically through carbohydrate limitation,¹⁹⁰ and ketogenic diet (KD), which is a high-fat diet with a low carbohydrate intake (typically <50 g CHO/day). Several studies have demonstrated that CR can reduce tumor growth of diverse tumor types, including breast,¹⁹¹ lung,¹⁹² prostate,¹⁹³ brain,¹⁹⁴ pancreatic,¹⁹⁵ and colorectal cancers.¹⁹⁶ Lien et al.,¹⁹⁷ studying both CR and KD, discovered that only CR prevents lung and pancreatic ductal adenocarcinoma mouse tumor allografts from growing. This means that additional processes help decrease progression of these tumors and lower the blood glucose

and insulin levels. In particular, the authors observed that CR changed the nutrient availability, which led to lower lipid levels in plasma and tumors, while they did not find it in KD. In the same study, the authors found that a diet low in carbohydrates and high in fats and protein consistently increased the overall survival time of pancreatic ductal adenocarcinoma patients. This occurred if fats and proteins were plant-based instead of animal-based, considering that the latter contains more saturated fats.¹⁹⁷ Instead, in a review by Zhu et al.,¹⁹⁸ the authors reported certain benefits of the KD including improved efficacy of many anticancer drugs in neuroblastoma, glioma, prostate, lung, pancreatic, bladder, endometrial, and breast cancers, as well as in acute myeloid leukemia. KD may also have a tumor growth-limiting effect in glioblastoma, colon, and breast cancers. This occurs because of its anti-inflammatory effect and the antitumor mechanisms of ketone bodies produced, besides lowering blood glucose levels.¹⁹⁹

Nevertheless, a high-fat diet (HFD), which, unlike KD, still contemplates considerable carbohydrate consumption, generally increases the incidence and growth of tumors, including colorectal,²⁰⁰ pancreatic,²⁰¹ prostate,²⁰² and hepatocellular carcinomas.²⁰³ Another similar diet, Western diet (WD), which is high in saturated fat and added sugars and low in fruits and vegetables, is linked to an increased risk of coronary artery disease (CAD), colon cancer, diseases with underlying oxidative stress, insulin resistance, AT inflammation, and lipid dysregulation, according to epidemiological studies.^{204,205}

Conversely, in massive general population cohorts, a diet with a high intake of fruits and vegetables has been correlated to a decreased risk of all-cause death and CAD events.²⁰⁶ As a result, many diets have been investigated for their ability to promote good health. One such diet is the Mediterranean diet, which emphasizes the consumption of whole grains, fruits, vegetables, legumes, seeds, and nuts. It also recommends the use of more olive oil and herbs as dish seasonings, and less butter and salt; it suggests to increase the consumption of fish and poultry and to decrease red meat. Additionally, it encourages people to eat more plant-based meals.²⁰⁷ In prospective studies, people with obesity who followed the Mediterranean diet saw improvements in circulating inflammatory markers, insulin sensitivity, and vascular function, which are metabolic syndrome indicators. These improvements lasted for up to 2 years.²⁰⁷ Significantly, a Mediterranean diet supplemented with extra-virgin olive oil in humans resulted in a lower incidence of breast cancer compared to the control group diet. This is probably because of the rich composition in polyphenols oleocanthal, oleuropein, hydroxytyrosol, and lignans of extra-virgin oil compared to other generic types of olive oil.²⁰⁸

Diets that are primarily plant-based, such as vegan and vegetarian diets, are associated with a lower risk of developing obesity, type 2 diabetes, ischemic heart disease, and some forms of cancer (gastrointestinal cancer for vegetarian diet and prostate cancer for vegan diet). A vegetarian diet involves avoiding the consumption of meat, poultry, fish, and their byproducts, while a vegan diet excludes all animal-derived products, including eggs, dairy products, and honey.²⁰⁹ These diets are characterized by a low-saturated fat intake and a high intake of fruits, vegetables, whole grains, legumes, soy products, nuts,

and seeds (all rich in fiber and phytochemicals), which seem to improve serum lipid profile and blood sugar control.²⁰⁹ The reduction of red meat intake has been associated with favorable outcomes.^{210,211} More specifically, the consumption of processed red meat was found to be associated with higher risk of colorectal cancer in two significant US cohorts.²¹²

Finally, fasting-mimicking diets (FMDs) are specially formulated dietary plans that are extremely low in calories (300 to 1100 kcal per day on average), sugars, and proteins. They mimic many of the effects of water-only fasting with improved patient compliance and lower nutritional risk.²¹³ According to Nencioni et al.,²¹⁴ FMD cycles could be useful to enhance the effects of cancer therapies in glioblastoma, mesothelioma, melanoma, fibrosarcoma, neuroblastoma, lung, breast, pancreatic, and colorectal cancers, activating anticancer immunosurveillance, such as tumor-infiltrating lymphocytes, reducing levels of glucose and leptin and increasing levels of adiponectin.

From these results, it is clear that the journey to find a sure answer about the role of different diets in the development of many tumors is still long and challenging.

5 | TARGETING LIPID METABOLISM AND ADIPOCYTES-BASED CELL THERAPY IN ONCOLOGY

5.1 | Lipid metabolism-targeted agents

Obese CAAs can affect the efficacy of anticancer treatment by preventing tumor drug penetration, altering lipid-based metabolism, causing drug resistance in tumor cells, increasing abnormal vasculature, impairing immune cell function, and supporting tumor cell survival.²¹⁵ Therefore, blocking these mechanisms is a novel promising strategy to develop innovative cancer therapies targeting the TME.²¹⁶

In particular, the patients with obesity have been shown to exhibit a poor outcome after traditional treatments including radiation, chemotherapy, and surgery for cancer, because of a deficient wound healing process, necessary for the latter type of therapy. Studies on how high adiposity affects radiotherapy have shown that a higher BMI is strongly correlated with its reduced efficacy.²¹⁷ However, obesity seemed to be associated with improved outcomes after treatment with immune checkpoint inhibitors. This has been called “the obesity paradox,” and the principal theory related to this phenomenon is the ability of AT to modify the phenotype of immune cells in a dysfunctional profile that is susceptible to treatment because of increased expression of the PD-1 target molecule.²¹⁷ The metabolic environment linked to obesity triggers monocytes to transform into tumor-associated macrophages, leading to chemoresistance and unfavorable response to chemotherapy, which are further mediated by adipocytes acquiring stem-like features. These elements are important modulators of cell proliferation, neoangiogenesis, and inflammation, which favor cancer initiation and progression, as well as chemoresistance.²¹⁸

One of the first solutions proposed to overcome complications correlated to obesity, was to combine well-known, affordable, and safe metabolic therapies with current cancer therapies to increase their efficacy, for instance, using metabolic drugs that currently treat widespread illnesses like type 2 diabetes²¹⁹ and cardiovascular disease.²²⁰ These pathologies involve dysregulated lipid metabolism, and therapies that target these common pathways may offer chances to improve the effectiveness of cancer therapy. Proliferation of tumor cells would eventually be inhibited by depletion of lipids used for energy, and by boosting ROS levels, raising the sensitivity to additional stress and increasing therapeutic responsiveness.²²¹

Small-molecule inhibitors, which can provide enzyme inhibition with molecular specificity, are another interesting family of drugs discovered in recent years. Acetyl-CoA carboxylase (ACC), in particular, modulates *de novo* FA synthesis²²² and can be present in two isoforms (ACC1 and ACC2), which are encoded by the genes ACACA and ACACB, respectively. Small-molecule inhibitors of these two genes have been found and tested for their anticancer effects, with encouraging preclinical evidence. The ability of ND-646 to block both the ACACA and ACACB isoforms, thus stopping the growth of non-small cell lung cancer (NSCLC), was first reported in 2016.^{223,224} Another small-molecule inhibitor, the liver-specific ND-654, was studied in a murine model of hepatocellular carcinoma (HCC), and it was shown to hinder liver lipid synthesis, reducing tumor formation.²²⁵ Both of these drugs were evaluated in combination with standard chemotherapy and demonstrated synergic inhibition by decreasing tumor size and incidence compared to monotherapy.^{223,225}

Other studies focused on trying to develop small-molecule inhibitors of stearoyl-CoA desaturase (SCD), a crucial enzyme involved in the production of MUFAs from their precursors, SFAs.²²⁶ According to recent evidence, ovarian cancer cells die by ferroptosis and apoptosis when SCD1 is blocked. This might be related to changes in the composition of membrane phospholipids brought on by the SCD1 inhibitors MF-438 and CAY10566.²²⁷

Another appealing therapeutic strategy is targeting lipid uptake.¹³¹ Recent evidence has shown that CD36 is a viable therapeutic target in cells that begin to metastasize.⁵⁷ To mediate the specific transport of FAs into cells, CD36 needs co-transporters, which are often members of the FA transport protein (FATP)/SLC27A family.²²⁸ According to the study by Zhang et al.,¹³¹ FATPs are expressed by melanoma cells and are responsible for transporting lipids from adipocytes to tumor cells. Thus, melanoma cells co-expressing CD36 and FATPs may be more generally implicated in both tumor growth and invasion. This finding is supported by the discovery of a substantial positive connection between FATP1 expression and lipid content in tumor cells.¹³¹ Thrombospondin-1 is one of the ligands of CD36, and their bond can have anti-angiogenic function, contributing to cancer cell growth inhibition.²²⁹ Therefore, the anticancer properties of several thrombospondin analogs are now being investigated, including VT1021, which is undergoing phase I clinical trials for the treatment of several primary tumors (NCT03364400). Moreover, two distinct antibodies, FA6.152, which blocks all the activities of CD36, and JC61.3, which blocks only the uptake of FAs and LDLs, were both

proved to be efficient and specific for tumors with lymph node metastases.⁵⁷ Also targeting FABP4 has been demonstrated to be effective for the treatment of tumors metastasizing to visceral AT, such as ovarian, gastric, and colon cancers.⁵⁰ FABP4 was found to be substantially expressed only in cancer cells at the adipocyte interface in a co-culture model.⁵⁰ It is interesting to note that co-cultivating breast and colon cancer cells with adipocytes increased cancer cell production of FABP4. For this reason, it can be hypothesized that FABP4 inhibition would decrease FA uptake by cancer cells and slow tumor growth.⁵⁰

A potential clinical approach is to prevent cancer cells from using FAs as a source of energy. In particular, it has been demonstrated in colon and breast cancer cells that etomoxir, an irreversible inhibitor of carnitine palmitoyltransferase-1 (CPT-1) in the mitochondria, potentiated the effect of the tested anticancer drugs by blocking the β -oxidation of FAs causing reduction of ATP levels, ROS generation, and apoptosis, as well as a collection of some cytotoxic LCFAs.²³⁰ However, because of serious adverse effects, etomoxir clinical use is currently restricted.²³¹ Reversible CPT-1 inhibitors offer a different option along with fewer negative side effects. ST1326, a reversible CPT-1 inhibitor, has shown anticancer properties in numerous non-solid tumors.^{232,233} Moreover, there is pre-clinical evidence for the use of additional inhibitors of mitochondrial FAO, such as perhexiline (another CPT-1 inhibitor) and trimetazidine (an inhibitor of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase [LCTH], which catalyzes the last step in mitochondrial β -oxidation). However, these molecules are currently in registered clinical trials for cardiac pathologies and type 2 diabetes only.²²¹

As most cancers increase FA production, blocking this mechanism is a straightforward strategy to decrease the presence of FAs in cancer cells. Fatty acid synthase (FASN), a lipogenic gene, is often overexpressed in cancer cells and is a potential target for therapy.^{234,235} Many studies have shown that FAS activity inhibition leads to apoptosis in cancer cells. The FAS action could be blocked by different therapeutic substances. For example, cerulenin permanently alters the target enzyme function²³⁶ although it is not selective for FAS.²³⁷ The first synthetic FAS-I inhibitor with notable anticancer action is C75.²³⁴ However, C75 causes significant weight loss in animals, and it induces anorexia in proportion to the dose increase. Lately, C93 has been characterized as a more specific FAS inhibitor.²³⁶ Orlistat is an oral medication that inhibits the thioesterase domain of FAS and is used for managing obesity.²³⁶ It can induce apoptosis in various cancer cell lines, but this does not occur in not normal cells.²³⁶

Finally, TVB-3166 and TVB-3664 are well-tolerated molecules that selectively inhibit FASN. This, in turn, suppresses the PI3K-Akt-mTOR pathway and β -catenin signaling to hinder cancer cell growth and promote their death.²³⁸

5.2 | Adipocyte-based cell therapy

In recent years, adipocytes have been effectively used as vectors for anticancer drugs. The adipocyte-based delivery system shares features with other cell-based systems, including high biocompatibility,

prolonged circulation in vivo after systemic injection, and strong affinity towards tumors and inflammatory areas. Furthermore, hydrophobic medicines can be effectively encapsulated because of the presence of lipids in adipocytes. Lipid droplets can gather during the lipolysis process triggered by tumor cells to support their metabolism, and this can be used as a “Trojan horse” method to provide local and long-lasting delivery of various drugs at the tumor sites.²³⁹ As an example, Wen et al.²⁴⁰ engineered adipocytes to act as a reservoir to transport anticancer drugs at the tumor sites by taking advantage of lipid metabolism. They discovered that adipocytes loaded with a ROS-responsive doxorubicin prodrug (pDOX) and ruminic acid (RA) might negatively affect tumor cells by activating the lipid metabolic pathway controlled by FABP4. Likewise, Aoki et al.²⁴¹ created a drug delivery system (DDS) based on ASCs that carried poly lactic-co-glycolic acid (PLGA), conjugated with pirarubicin. Pirarubicin has an inhibitory activity on DNA replication and can release anti-pancreatic cancer factors. Thanks to the infiltration of ASCs into the tumor site and to the dual effect of released pirarubicin, pir-PLGA nanoparticles (NPs) encapsulated in ASCs were able to inhibit the growth of pancreatic tumors, causing cancer cell apoptosis. In addition, when compared to pirarubicin treatment alone, pir-PLGA NP-loaded ASCs inhibited tumor development at very low doses with few side effects.

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

Adipocytes and AT have been recognized to play a crucial role in tumor development and progression. Adipocytes close to or distant from tumors establish a vicious cycle with cancer cells through adipokines, exosomes, lipids, and fatty acids exchange, promoting tumor growth, progression, metastasis, and resistance to therapy. Adipokines can act by stimulating pathways involved in cancer cell adhesion, migration, invasion, angiogenesis, and inflammation. FAs and lipids supply the cells growing need for metabolic substrates in support of proliferation and function as mediators or signaling molecules. Cancer cells, in turn, can reprogram adipocytes towards a more inflammatory state stimulating the release of lipids and the secretion of adipokines and chemokines. These mechanisms are enhanced in obesity, which is associated with an increased risk of developing certain cancers; this is also probably because of the intense use of lipids by tumor cells. For all these reasons, increasing effort has been addressed to understand mechanisms that lead to obesity, and novel therapeutic strategies based on the targeting of cancer metabolism are under preclinical and clinical development. The direction taken is promising but we must consider that responses can be highly variable, depending on the tumor types. The mapping of specific vulnerabilities to the different metabolic inhibitors for each tumor type, as well as the identification of potential synergistic effects with standard therapies, is required.

Diet is crucial in this context, providing the correct balance of lipids, which can have pro- or anti-inflammatory effects on the human body. However, nutritional interventions for cancer patients and close monitoring by nutritionists throughout treatment have not been fully

established. Understanding the mechanisms by which diet modifies the cancer cell metabolism and tumor features is challenging, considering the diet complexity. Therefore, we believe a prospective serum metabolome profiling of cancer patients under specific diet regimens would add important information. Finally, it is necessary to study the correlation between the metabolome of tumors and biological, molecular disease features, as well as patient clinical outcomes, including treatment response.

AUTHOR CONTRIBUTIONS

Chiara Calabrese and Chiara Liverani conceived, wrote, and edited the manuscript. Giacomo Miserocchi, Alessandro De Vita, Chiara Spadazzi, Claudia Cocchi, Silvia Vanni, Sofia Gabellone, Giovanni Martinelli, Nicoletta Ranallo, and Alberto Bongiovanni wrote the manuscript. Giacomo Miserocchi conceived and drafted the figures. All authors reviewed and approved the manuscript.

ACKNOWLEDGEMENTS

This work was supported by an Italian Ministry of Health Grant for the project GR-2019-12370014. The authors thank Marcia Jacqueline Myrie and Cristiano Verna for their editorial assistance. Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ORCID

Giacomo Miserocchi  <https://orcid.org/0000-0001-6618-1981>

Claudia Cocchi  <https://orcid.org/0000-0002-7736-9039>

REFERENCES

1. Lichtman MA. Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. *Oncologist*. 2010;15(10):1083-1101. doi:10.1634/theoncologist.2010-0206
2. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. *Lancet Oncol*. 2002;3(9):565-574. doi:10.1016/s1470-2045(02)00849-5
3. Klötting N, Blüher M. Adipocyte dysfunction, inflammation, and metabolic syndrome. *Rev Endocr Metab Disord*. 2014;15(4):277-287. doi:10.1007/s11154-014-9301-0
4. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer*. 2015;15(8):484-498. doi:10.1038/nrc3967
5. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer—viewpoint of the IARC working group. *N Engl J Med*. 2016;375(8):794-798. doi:10.1056/NEJMs1606602
6. Sung H, Siegel RL, Torre LA, et al. Global patterns in excess body weight and the associated cancer burden. *CA Cancer J Clin*. 2019;69(2):88-112. doi:10.3322/caac.21499
7. Hurwitz LM, Dogbe N, Barry KH, Koutros S, Berndt SI. Obesity and prostate cancer screening, incidence, and mortality in the prostate, lung, colorectal, and ovarian cancer screening trial. *J Natl Cancer Inst*. 2023;115(12):1506-1514. doi:10.1093/jnci/djad113

8. Nieman KM, Romero IL, Van Houten B, Lengyel E. Adipose tissue and adipocytes support tumorigenesis and metastasis. *Biochim Biophys Acta*. 2013;1831(10):1533-1541. doi:10.1016/j.bbali.2013.02.010
9. Ose J, Holowatyj AN, Nattenmüller J, et al. Metabolomics profiling of visceral and abdominal subcutaneous adipose tissue in colorectal cancer patients: results from the ColoCare study. *Cancer Causes Control*. 2020;31(8):723-735. doi:10.1007/s10552-020-01312-1
10. Himbert C, Delphan M, Scherer D, Bowers LW, Hursting S, Ulrich CM. Signals from the adipose microenvironment and the obesity-cancer link—a systematic review. *Cancer Prev Res (Phila)*. 2017;10(9):494-506. doi:10.1158/1940-6207.CAPR-16-0322
11. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer*. 2014;14(11):754-762. doi:10.1038/nrc3829
12. Gimple RC, Kidwell RL, Kim LJY, et al. Glioma stem cell-specific Superenhancer promotes polyunsaturated fatty-acid synthesis to support EGFR signaling. *Cancer Discov*. 2019;9(9):1248-1267. doi:10.1158/2159-8290.CD-19-0061
13. Talebi A, Dehairs J, Rambow F, et al. Sustained SREBP-1-dependent lipogenesis as a key mediator of resistance to BRAF-targeted therapy. *Nat Commun*. 2018;9(1):2500. doi:10.1038/s41467-018-04664-0
14. Attané C, Muller C. Drilling for oil: tumor-surrounding adipocytes fueling cancer. *Trends Cancer*. 2020;6(7):593-604. doi:10.1016/j.trecan.2020.03.001
15. Dirat BA, Bochet L, Escourrou G, Valet P, Muller C. Unraveling the obesity and breast cancer links: a role for cancer-associated adipocytes. *Endocr Dev*. 2010;19:45-52. doi:10.1159/000316896
16. Incio J, Liu H, Suboj P, et al. Obesity-induced inflammation and desmoplasia promote pancreatic cancer progression and resistance to chemotherapy. *Cancer Discov*. 2016;6(8):852-869. doi:10.1158/2159-8290.CD-15-1177
17. Lenz A, Diamond FB Jr. Obesity: the hormonal milieu. *Curr Opin Endocrinol Diabetes Obes*. 2008;15(1):9-20. doi:10.1097/MED.0b013e3282f43a5b
18. Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. *Physiol Rev*. 2015;95(3):727-748. doi:10.1152/physrev.00030.2014
19. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest*. 2011;121(6):2111-2117. doi:10.1172/JCI57132
20. Park J, Morley TS, Kim M, Clegg DJ, Scherer PE. Obesity and cancer—mechanisms underlying tumour progression and recurrence. *Nat Rev Endocrinol*. 2014;10(8):455-465. doi:10.1038/nrendo.2014.94
21. Wang D, Dubois RN. Eicosanoids and cancer. *Nat Rev Cancer*. 2010;10(3):181-193. doi:10.1038/nrc2809
22. Hisano Y, Hla T. Bioactive lysolipids in cancer and angiogenesis. *Pharmacol Ther*. 2019;193:91-98. doi:10.1016/j.pharmthera.2018.07.006
23. Mayne ST, Playdon MC, Rock CL. Diet, nutrition, and cancer: past, present and future. *Nat Rev Clin Oncol*. 2016;13(8):504-515. doi:10.1038/nrclinonc.2016.24
24. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. *Nat Rev Cancer*. 2011;11(12):886-895. doi:10.1038/nrc3174
25. Meynet O, Ricci JE. Caloric restriction and cancer: molecular mechanisms and clinical implications. *Trends Mol Med*. 2014;20(8):419-427. doi:10.1016/j.molmed.2014.05.001
26. Lien EC, Vander Heiden MG. A framework for examining how diet impacts tumour metabolism. *Nat Rev Cancer*. 2019;19(11):651-661. doi:10.1038/s41568-019-0198-5
27. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*. 2009;324(5930):1029-1033. doi:10.1126/science.1160809
28. Liberti MV, Locasale JW. Correction to: 'The Warburg effect: how does it benefit cancer cells?': [trends in biochemical sciences, 41 (2016) 211]. *Trends Biochem Sci*. 2016;41(3):287. doi:10.1016/j.tibs.2016.01.004
29. Martinez-Outschoorn UE, Peiris-Pagés M, Pestell RG, Sotgia F, Lisanti MP. Cancer metabolism: a therapeutic perspective. *Nat Rev Clin Oncol*. 2017;14(2):113. doi:10.1038/nrclinonc.2017.1
30. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. *Cell Metab*. 2016;23(1):27-47. doi:10.1016/j.cmet.2015.12.006
31. Dey P, Kimmelman AC, DePinho RA. Metabolic codependencies in the tumor microenvironment. *Cancer Discov*. 2021;11(5):1067-1081. doi:10.1158/2159-8290.CD-20-1211
32. Place AE, Jin Huh S, Polyak K. The microenvironment in breast cancer progression: biology and implications for treatment. *Breast Cancer Res*. 2011;13(6):227. doi:10.1186/bcr2912
33. Pavlides S, Whitaker-Menezes D, Castello-Cros R, et al. The reverse Warburg effect: aerobic glycolysis in cancer associated fibroblasts and the tumor stroma. *Cell Cycle*. 2009;8(23):3984-4001. doi:10.4161/cc.8.23.10238
34. Fiaschi T, Marini A, Giannoni E, et al. Reciprocal metabolic reprogramming through lactate shuttle coordinately influences tumor-stroma interplay. *Cancer Res*. 2012;72(19):5130-5140. doi:10.1158/0008-5472.CAN-12-1949
35. Feng J, Yang H, Zhang Y, et al. Tumor cell-derived lactate induces TAZ-dependent upregulation of PD-L1 through GPR81 in human lung cancer cells. *Oncogene*. 2017;36(42):5829-5839. doi:10.1038/onc.2017.188
36. Kalluri R. The biology and function of fibroblasts in cancer. *Nat Rev Cancer*. 2016;16(9):582-598. doi:10.1038/nrc.2016.73
37. Martinez-Outschoorn UE, Pavlides S, Howell A, et al. Stromal-epithelial metabolic coupling in cancer: integrating autophagy and metabolism in the tumor microenvironment. *Int J Biochem Cell Biol*. 2011;43(7):1045-1051. doi:10.1016/j.biocel.2011.01.023
38. Sharma D, Singh M, Rani R. Role of LDH in tumor glycolysis: regulation of LDHA by small molecules for cancer therapeutics. *Semin Cancer Biol*. 2022;87:184-195. doi:10.1016/j.semcancer.2022.11.007
39. Galluzzi L, Kepp O, Vander Heiden MG, Kroemer G. Metabolic targets for cancer therapy [published correction appears in *Nat Rev Drug Discov*. 2013 Dec;12(12):963]. *Nat Rev Drug Discov*. 2013;12(11):829-846. doi:10.1038/nrd4145
40. Chajès V, Cambot M, Moreau K, Lenoir GM, Joulin V. Acetyl-CoA carboxylase alpha is essential to breast cancer cell survival. *Cancer Res*. 2006;66(10):5287-5294. doi:10.1158/0008-5472.CAN-05-1489
41. Flavin R, Peluso S, Nguyen PL, Loda M. Fatty acid synthase as a potential therapeutic target in cancer. *Future Oncol*. 2010;6(4):551-562. doi:10.2217/fon.10.11
42. Saffransova L, Hložkova K, Starkova J. Targeting amino acid metabolism in cancer. *Int Rev Cell Mol Biol*. 2022;373:37-79. doi:10.1016/bs.ircmb.2022.08.001
43. Hishikawa D, Hashidate T, Shimizu T, Shindou H. Diversity and function of membrane glycerophospholipids generated by the remodeling pathway in mammalian cells [published correction appears in *J Lipid Res*. 2014 Nov;55(11):2444]. *J Lipid Res*. 2014;55(5):799-807. doi:10.1194/jlr.R046094
44. Park JB, Lee CS, Jang JH, et al. Phospholipase signalling networks in cancer. *Nat Rev Cancer*. 2012;12(11):782-792. doi:10.1038/nrc3379
45. Ekambaram P, Lambiv W, Cazzolli R, Ashton AW, Honn KV. The thromboxane synthase and receptor signaling pathway in cancer: an emerging paradigm in cancer progression and metastasis. *Cancer*

- Metastasis Rev.* 2011;30(3-4):397-408. doi:[10.1007/s10555-011-9297-9](https://doi.org/10.1007/s10555-011-9297-9)
46. Fabian CJ, Kimler BF, Hursting SD. Omega-3 fatty acids for breast cancer prevention and survivorship. *Breast Cancer Res.* 2015;17(1):62. doi:[10.1186/s13058-015-0571-6](https://doi.org/10.1186/s13058-015-0571-6)
 47. Wang YY, Attané C, Milhas D, et al. Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells. *JCI Insight.* 2017;2(4):e87489. doi:[10.1172/jci.insight.87489](https://doi.org/10.1172/jci.insight.87489)
 48. Bochet L, Lehuédé C, Dauvillier S, et al. Adipocyte-derived fibroblasts promote tumor progression and contribute to the desmoplastic reaction in breast cancer. *Cancer Res.* 2013;73(18):5657-5668. doi:[10.1158/0008-5472.CAN-13-0530](https://doi.org/10.1158/0008-5472.CAN-13-0530)
 49. Gazi E, Gardner P, Lockyer NP, Hart CA, Brown MD, Clarke NW. Direct evidence of lipid translocation between adipocytes and prostate cancer cells with imaging FTIR microspectroscopy. *J Lipid Res.* 2007;48(8):1846-1856. doi:[10.1194/jlr.M700131-JLR200](https://doi.org/10.1194/jlr.M700131-JLR200)
 50. Nieman KM, Kenny HA, Penicka CV, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nat Med.* 2011;17(11):1498-1503. doi:[10.1038/nm.2492](https://doi.org/10.1038/nm.2492)
 51. Dirat B, Bochet L, Dabek M, et al. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. *Cancer Res.* 2011;71(7):2455-2465. doi:[10.1158/0008-5472.CAN-10-3323](https://doi.org/10.1158/0008-5472.CAN-10-3323)
 52. Santander AM, Lopez-Ocejo O, Casas O, et al. Paracrine interactions between adipocytes and tumor cells recruit and modify macrophages to the mammary tumor microenvironment: the role of obesity and inflammation in breast adipose tissue. *Cancers (Basel).* 2015;7(1):143-178. doi:[10.3390/cancers7010143](https://doi.org/10.3390/cancers7010143)
 53. Delort L, Lequeux C, Dubois V, et al. Reciprocal interactions between breast tumor and its adipose microenvironment based on a 3D adipose equivalent model. *PLoS ONE.* 2013;8(6):e66284. doi:[10.1371/journal.pone.0066284](https://doi.org/10.1371/journal.pone.0066284)
 54. Lapeire L, Hendrix A, Lambein K, et al. Cancer-associated adipose tissue promotes breast cancer progression by paracrine oncostatin M and Jak/STAT3 signaling. *Cancer Res.* 2014;74(23):6806-6819. doi:[10.1158/0008-5472.CAN-14-0160](https://doi.org/10.1158/0008-5472.CAN-14-0160)
 55. Kamphorst JJ, Cross JR, Fan J, et al. Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. *Proc Natl Acad Sci U S A.* 2013;110(22):8882-8887. doi:[10.1073/pnas.1307237110](https://doi.org/10.1073/pnas.1307237110)
 56. Ladanyi A, Mukherjee A, Kenny HA, et al. Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis. *Oncogene.* 2018;37(17):2285-2301. doi:[10.1038/s41388-017-0093-z](https://doi.org/10.1038/s41388-017-0093-z)
 57. Pascual G, Avgustinova A, Mejetta S, et al. Targeting metastasis-initiating cells through the fatty acid receptor CD36. *Nature.* 2017;541(7635):41-45. doi:[10.1038/nature20791](https://doi.org/10.1038/nature20791)
 58. Guillaumond F, Bidaut G, Ouaisi M, et al. Cholesterol uptake disruption, in association with chemotherapy, is a promising combined metabolic therapy for pancreatic adenocarcinoma. *Proc Natl Acad Sci U S A.* 2015;112(8):2473-2478. doi:[10.1073/pnas.1421601112](https://doi.org/10.1073/pnas.1421601112)
 59. Corbet C, Pinto A, Martherus R, Santiago de Jesus JP, Polet F, Feron O. Acidosis drives the reprogramming of fatty acid metabolism in cancer cells through changes in mitochondrial and histone acetylation. *Cell Metab.* 2016;24(2):311-323. doi:[10.1016/j.cmet.2016.07.003](https://doi.org/10.1016/j.cmet.2016.07.003)
 60. Ren Y, Shen HM. Critical role of AMPK in redox regulation under glucose starvation. *Redox Biol.* 2019;25:101154. doi:[10.1016/j.redox.2019.101154](https://doi.org/10.1016/j.redox.2019.101154)
 61. Padanad MS, Konstantinidou G, Venkateswaran N, et al. Fatty acid oxidation mediated by acyl-CoA synthetase long chain 3 is required for mutant KRAS lung tumorigenesis. *Cell Rep.* 2016;16(6):1614-1628. doi:[10.1016/j.celrep.2016.07.009](https://doi.org/10.1016/j.celrep.2016.07.009)
 62. Camarda R, Zhou AY, Kohnz RA, et al. Inhibition of fatty acid oxidation as a therapy for MYC-overexpressing triple-negative breast cancer. *Nat Med.* 2016;22(4):427-432. doi:[10.1038/nm.4055](https://doi.org/10.1038/nm.4055)
 63. Ma Y, Temkin SM, Hawkrigde AM, et al. Fatty acid oxidation: an emerging facet of metabolic transformation in cancer. *Cancer Lett.* 2018;435:92-100. doi:[10.1016/j.canlet.2018.08.006](https://doi.org/10.1016/j.canlet.2018.08.006)
 64. Lin H, Patel S, Affleck VS, et al. Fatty acid oxidation is required for the respiration and proliferation of malignant glioma cells. *Neuro Oncol.* 2017;19(1):43-54. doi:[10.1093/neuonc/now128](https://doi.org/10.1093/neuonc/now128)
 65. Yang H, Deng Q, Ni T, et al. Targeted inhibition of LPL/FABP4/CPT1 fatty acid metabolic axis can effectively prevent the progression of nonalcoholic steatohepatitis to liver cancer. *Int J Biol Sci.* 2021;17(15):4207-4222. doi:[10.7150/ijbs.64714](https://doi.org/10.7150/ijbs.64714)
 66. Li Z, Liu H, He J, et al. Acetyl-CoA synthetase 2: a critical linkage in obesity-induced tumorigenesis in myeloma. *Cell Metab.* 2021;33(1):78-93.e7. doi:[10.1016/j.cmet.2020.12.011](https://doi.org/10.1016/j.cmet.2020.12.011)
 67. Pietrocola F, Galluzzi L, Bravo-San Pedro JM, Madeo F, Kroemer G. Acetyl coenzyme A: a central metabolite and second messenger. *Cell Metab.* 2015;21(6):805-821. doi:[10.1016/j.cmet.2015.05.014](https://doi.org/10.1016/j.cmet.2015.05.014)
 68. Comerford SA, Huang Z, Du X, et al. Acetate dependence of tumors. *Cell.* 2014;159(7):1591-1602. doi:[10.1016/j.cell.2014.11.020](https://doi.org/10.1016/j.cell.2014.11.020)
 69. Schug ZT, Peck B, Jones DT, et al. Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress. *Cancer Cell.* 2015;27(1):57-71. doi:[10.1016/j.ccell.2014.12.002](https://doi.org/10.1016/j.ccell.2014.12.002)
 70. Ghaben AL, Scherer PE. Adipogenesis and metabolic health. *Nat Rev Mol Cell Biol.* 2019;20(4):242-258. doi:[10.1038/s41580-018-0093-z](https://doi.org/10.1038/s41580-018-0093-z)
 71. Yang A, Mottillo EP. Adipocyte lipolysis: from molecular mechanisms of regulation to disease and therapeutics. *Biochem J.* 2020;477(5):985-1008. doi:[10.1042/BCJ20190468](https://doi.org/10.1042/BCJ20190468)
 72. Chait A, den Hartigh LJ. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. *Front Cardiovasc Med.* 2020;7:22. doi:[10.3389/fcvm.2020.00022](https://doi.org/10.3389/fcvm.2020.00022)
 73. Edens NK, Leibel RL, Hirsch J. Mechanism of free fatty acid esterification in human adipocytes in vitro. *J Lipid Res.* 1990;31(8):1423-1431. doi:[10.1016/S0022-2275\(20\)42613-6](https://doi.org/10.1016/S0022-2275(20)42613-6)
 74. Zechner R, Zimmermann R, Eichmann TO, et al. FAT SIGNALS--lipases and lipolysis in lipid metabolism and signaling. *Cell Metab.* 2012;15(3):279-291. doi:[10.1016/j.cmet.2011.12.018](https://doi.org/10.1016/j.cmet.2011.12.018)
 75. Park YK, Lee TY, Choi JS, et al. Inhibition of adipogenesis and leptin production in 3T3-L1 adipocytes by a derivative of meridianin C. *Biochem Biophys Res Commun.* 2014;452(4):1078-1083. doi:[10.1016/j.bbrc.2014.09.050](https://doi.org/10.1016/j.bbrc.2014.09.050)
 76. Proença AR, Sertié RA, Oliveira AC, et al. New concepts in white adipose tissue physiology. *Braz J Med Biol Res.* 2014;47(3):192-205. doi:[10.1590/1414-431X20132911](https://doi.org/10.1590/1414-431X20132911)
 77. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol.* 2011;11(2):85-97. doi:[10.1038/nri2921](https://doi.org/10.1038/nri2921)
 78. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003;112(12):1796-1808. doi:[10.1172/JCI19246](https://doi.org/10.1172/JCI19246)
 79. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res.* 2005;96(9):939-949. doi:[10.1161/01.RES.0000163635.62927.34](https://doi.org/10.1161/01.RES.0000163635.62927.34)
 80. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med.* 2010;61(1):301-316. doi:[10.1146/annurev.med.080708.082713](https://doi.org/10.1146/annurev.med.080708.082713)
 81. Ziech D, Franco R, Pappa A, Panayiotidis MI. Reactive oxygen species (ROS)-induced genetic and epigenetic alterations in human carcinogenesis. *Mutat Res.* 2011;711(1-2):167-173. doi:[10.1016/j.mrfmmm.2011.02.015](https://doi.org/10.1016/j.mrfmmm.2011.02.015)
 82. Mantzoros CS, Magkos F, Brinkoetter M, et al. Leptin in human physiology and pathophysiology. *Am J Physiol Endocrinol Metab.* 2011;301(4):E567-E584. doi:[10.1152/ajpendo.00315.2011](https://doi.org/10.1152/ajpendo.00315.2011)

83. Barone I, Giordano C, Bonfiglio D, Andò S, Catalano S. The weight of obesity in breast cancer progression and metastasis: clinical and molecular perspectives. *Semin Cancer Biol.* 2020;60:274-284. doi:10.1016/j.semcancer.2019.09.001
84. Cirillo D, Rachiglio AM, la Montagna R, Giordano A, Normanno N. Leptin signaling in breast cancer: an overview. *J Cell Biochem.* 2008;105(4):956-964. doi:10.1002/jcb.21911
85. Mauro L, Catalano S, Bossi G, et al. Evidences that leptin up-regulates E-cadherin expression in breast cancer: effects on tumor growth and progression. *Cancer Res.* 2007;67(7):3412-3421. doi:10.1158/0008-5472.CAN-06-2890
86. Perera CN, Chin HG, Duru N, Camarillo IG. Leptin-regulated gene expression in MCF-7 breast cancer cells: mechanistic insights into leptin-regulated mammary tumor growth and progression [published correction appears in *J Endocrinol.* 2008 Dec;199(3):499]. *J Endocrinol.* 2008;199(2):221-233. doi:10.1677/JOE-08-0215
87. Onuma M, Bub JD, Rummel TL, Iwamoto Y. Prostate cancer cell-adipocyte interaction: leptin mediates androgen-independent prostate cancer cell proliferation through c-Jun NH2-terminal kinase. *J Biol Chem.* 2003;278(43):42660-42667. doi:10.1074/jbc.M304984200
88. Stefanou N, Papanikolaou V, Furukawa Y, Nakamura Y, Tsezou A. Leptin as a critical regulator of hepatocellular carcinoma development through modulation of human telomerase reverse transcriptase. *BMC Cancer.* 2010;10:442. doi:10.1186/1471-2407-10-442
89. Nakajima TE, Yamada Y, Hamano T, et al. Adipocytokine levels in gastric cancer patients: resistin and visfatin as biomarkers of gastric cancer. *J Gastroenterol.* 2009;44(7):685-690. doi:10.1007/s00535-009-0063-5
90. Wågsäter D, Mumtaz M, Lofgren S, Hugander A, Dimberg J. Resistin in human colorectal cancer: increased expression independently of resistin promoter -420C > G genotype. *Cancer Invest.* 2008;26(10):1008-1014. doi:10.1080/07357900802087267
91. Miethe C, Torres L, Beristain J, Zamora M, Price RS. The role of visfatin and resistin in an in vitro model of obesity-induced invasive liver cancer. *Can J Physiol Pharmacol.* 2021;99(9):839-846. doi:10.1139/cjpp-2020-0377
92. Zhang M, Yan L, Wang GJ, Jin R. Resistin effects on pancreatic cancer progression and chemoresistance are mediated through its receptors CAP1 and TLR4 [retracted in *J Cell Physiol.* 2022 Feb;237(2):1632]. *J Cell Physiol.* 2019;234(6):9457-9466. doi:10.1002/jcp.27631
93. Parafiniuk K, Skiba W, Pawłowska A, Suszczyk D, Maciejczyk A, Wertel I. The role of the adipokine resistin in the pathogenesis and progression of epithelial ovarian cancer. *Biomedicine.* 2022;10(4):920. doi:10.3390/biomedicines10040920
94. Lee YC, Chen YJ, Wu CC, Lo S, Hou MF, Yuan SS. Resistin expression in breast cancer tissue as a marker of prognosis and hormone therapy stratification. *Gynecol Oncol.* 2012;125(3):742-750. doi:10.1016/j.ygyno.2012.02.032
95. Zhao CC, Chen J, Niu RF, Liu Y, Zhang CG. Increased resistin suggests poor prognosis and promotes development of lung adenocarcinoma [retracted in: *Oncol rep.* 2023 Aug;50(2)]. *Oncol Rep.* 2018;40(6):3392-3404. doi:10.3892/or.2018.6736
96. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol.* 2014;15(3):178-196. doi:10.1038/nrm3758
97. Wang CH, Wang PJ, Hsieh YC, et al. Resistin facilitates breast cancer progression via TLR4-mediated induction of mesenchymal phenotypes and stemness properties. *Oncogene.* 2018;37(5):589-600. doi:10.1038/ncr.2017.357
98. Avtanski D, Garcia A, Caraballo B, et al. In vitro effects of resistin on epithelial to mesenchymal transition (EMT) in MCF-7 and MDA-MB-231 breast cancer cells—qRT-PCR and Western blot analyses data. *Data Brief.* 2019;25:104118. doi:10.1016/j.dib.2019.104118
99. Tian YF, Chu CH, Wu MH, et al. Anthropometric measures, plasma adiponectin, and breast cancer risk. *Endocr Relat Cancer.* 2007;14(3):669-677. doi:10.1677/ERC-06-0089
100. Sher DJ, Oh WK, Jacobus S, Regan MM, Lee GS, Mantzoros C. Relationship between serum adiponectin and prostate cancer grade. *Prostate.* 2008;68(14):1592-1598. doi:10.1002/pros.20823
101. Nagaraju GP, Aliya S, Alese OB. Role of adiponectin in obesity related gastrointestinal carcinogenesis. *Cytokine Growth Factor Rev.* 2015;26(1):83-93. doi:10.1016/j.cytogfr.2014.06.007
102. Cust AE, Kaaks R, Friedenreich C, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *J Clin Endocrinol Metab.* 2007;92(1):255-263. doi:10.1210/jc.2006-1371
103. Sharma D, Wang J, Fu PP, et al. Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. *Hepatology.* 2010;52(5):1713-1722. doi:10.1002/hep.23892
104. Park EJ, Lee JH, Yu GY, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell.* 2010;140(2):197-208. doi:10.1016/j.cell.2009.12.052
105. Taniguchi K, Karin M. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. *Semin Immunol.* 2014;26(1):54-74. doi:10.1016/j.smim.2014.01.001
106. Heinrich PC, Behrmann I, Haan S, Hermans HM, Müller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem J.* 2003;374(Pt 1):1-20. doi:10.1042/BJ20030407
107. Rauti R, Rusolo F, Sharma A, Colonna G, Castello G, Costantini S. Functional and structural features of adipokine family. *Cytokine.* 2013;61(1):1-14. doi:10.1016/j.cyto.2012.08.036
108. Guadagni F, Ferroni P, Palmirotta R, Portarena I, Formica V, Roselli M. Review. TNF/VEGF cross-talk in chronic inflammation-related cancer initiation and progression: an early target in anticancer therapeutic strategy. *In Vivo.* 2007;21(2):147-161.
109. Lu X, Kang Y. Chemokine (C-C motif) ligand 2 engages CCR2+ stromal cells of monocytic origin to promote breast cancer metastasis to lung and bone. *J Biol Chem.* 2009;284(42):29087-29096. doi:10.1074/jbc.M109.035899
110. Melgarejo E, Medina MA, Sánchez-Jiménez F, Urdiales JL. Monocyte chemoattractant protein-1: a key mediator in inflammatory processes. *Int J Biochem Cell Biol.* 2009;41(5):998-1001. doi:10.1016/j.biocel.2008.07.018
111. Zhang J, Lu Y, Pienta KJ. Multiple roles of chemokine (C-C motif) ligand 2 in promoting prostate cancer growth. *J Natl Cancer Inst.* 2010;102(8):522-528. doi:10.1093/jnci/djq044
112. Yasui H, Kajiyama H, Tamauchi S, et al. CCL2 secreted from cancer-associated mesothelial cells promotes peritoneal metastasis of ovarian cancer cells through the P38-MAPK pathway. *Clin Exp Metastasis.* 2020;37(1):145-158. doi:10.1007/s10585-019-09993-y
113. Izumi K, Fang LY, Mizokami A, et al. Targeting the androgen receptor with siRNA promotes prostate cancer metastasis through enhanced macrophage recruitment via CCL2/CCR2-induced STAT3 activation. *EMBO Mol Med.* 2013;5(9):1383-1401. doi:10.1002/emmm.201202367
114. Arendt LM, McCreedy J, Keller PJ, et al. Obesity promotes breast cancer by CCL2-mediated macrophage recruitment and angiogenesis. *Cancer Res.* 2013;73(19):6080-6093. doi:10.1158/0008-5472.CAN-13-0926
115. Liu Q, Song J, Pan Y, et al. Wnt5a/CaMKII/ERK/CCL2 axis is required for tumor-associated macrophages to promote colorectal cancer progression. *Int J Biol Sci.* 2020;16(6):1023-1034. doi:10.7150/ijbs.40535
116. Ding M, He SJ, Yang J. MCP-1/CCL2 mediated by autocrine loop of PDGF-BB promotes invasion of lung cancer cell by recruitment of

- macrophages via CCL2-CCR2 axis. *J Interferon Cytokine Res.* 2019; 39(4):224-232. doi:10.1089/jir.2018.0113
117. Zhuang H, Cao G, Kou C, Liu T. CCL2/CCR2 axis induces hepatocellular carcinoma invasion and epithelial-mesenchymal transition in vitro through activation of the hedgehog pathway. *Oncol Rep.* 2018;39(1):21-30. doi:10.3892/or.2017.6069
 118. Sanford DE, Belt BA, Panni RZ, et al. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. *Clin Cancer Res.* 2013;19(13):3404-3415. doi:10.1158/1078-0432.CCR-13-0525
 119. Arakaki R, Yamasaki T, Kanno T, et al. CCL2 as a potential therapeutic target for clear cell renal cell carcinoma. *Cancer Med.* 2016;5(10):2920-2933. doi:10.1002/cam4.886
 120. Chen CH, Su LJ, Tsai HT, Hwang CF. ELF-1 expression in nasopharyngeal carcinoma facilitates proliferation and metastasis of cancer cells via modulation of CCL2/CCR2 signaling. *Cancer Manag Res.* 2019;11:5243-5254. Published 2019 Jun 6. doi:10.2147/CMAR.S196355
 121. Harvey AE, Lashinger LM, Hursting SD. The growing challenge of obesity and cancer: an inflammatory issue. *Ann N Y Acad Sci.* 2011; 1229(1):45-52. doi:10.1111/j.1749-6632.2011.06096.x
 122. Vona-Davis L, Rose DP. Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression. *Endocr Relat Cancer.* 2007;14(2):189-206. doi:10.1677/ERC-06-0068
 123. Sánchez-Jiménez F, Pérez-Pérez A, de la Cruz-Merino L, Sánchez-Margalet V. Obesity and breast cancer: role of leptin. *Front Oncol.* 2019;9:596. doi:10.3389/fonc.2019.00596
 124. Pérez-Hernández AI, Catalán V, Gómez-Ambrosi J, Rodríguez A, Frühbeck G. Mechanisms linking excess adiposity and carcinogenesis promotion. *Front Endocrinol (Lausanne).* 2014;5:65. doi:10.3389/fendo.2014.00065
 125. Bouche C, Quail DF. Fueling the tumor microenvironment with cancer-associated adipocytes. *Cancer Res.* 2023;83(8):1170-1172. doi:10.1158/0008-5472.CAN-23-0505
 126. Wang YY, Lehuédé C, Laurent V, et al. Adipose tissue and breast epithelial cells: a dangerous dynamic duo in breast cancer. *Cancer Lett.* 2012;324(2):142-151. doi:10.1016/j.canlet.2012.05.019
 127. Wu Q, Li B, Li Z, Li J, Sun S, Sun S. Cancer-associated adipocytes: key players in breast cancer progression. *J Hematol Oncol.* 2019; 12(1):95. doi:10.1186/s13045-019-0778-6
 128. Zhu Q, Zhu Y, Hepler C, et al. Adipocyte mesenchymal transition contributes to mammary tumor progression. *Cell Rep.* 2022;40(11):111362. doi:10.1016/j.celrep.2022.111362
 129. Dumas JF, Brisson L. Interaction between adipose tissue and cancer cells: role for cancer progression. *Cancer Metastasis Rev.* 2021;40(1):31-46. doi:10.1007/s10555-020-09934-2
 130. Takehara M, Sato Y, Kimura T, et al. Cancer-associated adipocytes promote pancreatic cancer progression through SAA1 expression. *Cancer Sci.* 2020;111(8):2883-2894. doi:10.1111/cas.14527
 131. Zhang M, Di Martino JS, Bowman RL, et al. Adipocyte-derived lipids mediate melanoma progression via FATP proteins. *Cancer Discov.* 2018;8(8):1006-1025. doi:10.1158/2159-8290.CD-17-1371
 132. Rios-Colon L, Arthur E, Niture S, Qi Q, Moore JT, Kumar D. The role of exosomes in the crosstalk between adipocytes and liver cancer cells. *Cells.* 2020;9(9):1988. doi:10.3390/cells9091988
 133. Andarawewa KL, Motrescu ER, Chenard MP, et al. Stromelysin-3 is a potent negative regulator of adipogenesis participating to cancer cell-adipocyte interaction/crosstalk at the tumor invasive front. *Cancer Res.* 2005;65(23):10862-10871. doi:10.1158/0008-5472.CAN-05-1231
 134. Zhang Y, Daquinag AC, Amaya-Manzanares F, Sirin O, Tseng C, Kolonin MG. Stromal progenitor cells from endogenous adipose tissue contribute to pericytes and adipocytes that populate the tumor microenvironment. *Cancer Res.* 2012;72(20):5198-5208. doi:10.1158/0008-5472.CAN-12-0294
 135. Saha A, Kolonin MG, DiGiovanni J. Obesity and prostate cancer - microenvironmental roles of adipose tissue. *Nat Rev Urol.* 2023; 20(10):579-596. doi:10.1038/s41585-023-00764-9
 136. Zhang Y, Daquinag A, Traktuev DO, et al. White adipose tissue cells are recruited by experimental tumors and promote cancer progression in mouse models. *Cancer Res.* 2009;69(12):5259-5266. doi:10.1158/0008-5472.CAN-08-3444
 137. Kolonin MG, Anastassiou D. Adipose stromal cell-derived cancer-associated fibroblasts suppress FGFR inhibitor efficacy. *Cancer Res.* 2024;84(5):648-649. doi:10.1158/0008-5472.CAN-23-3904
 138. Huang-Doran I, Zhang CY, Vidal-Puig A. Extracellular vesicles: novel mediators of cell communication in metabolic disease. *Trends Endocrinol Metab.* 2017;28(1):3-18. doi:10.1016/j.tem.2016.10.003
 139. Milane L, Singh A, Mattheolabakis G, Suresh M, Amiji MM. Exosome mediated communication within the tumor microenvironment. *J Control Release.* 2015;219:278-294. doi:10.1016/j.jconrel.2015.06.029
 140. Tkach M, Théry C. Communication by extracellular vesicles: where we are and where we need to go. *Cell.* 2016;164(6):1226-1232. doi:10.1016/j.cell.2016.01.043
 141. Shah N, Ishii M, Brandon C, et al. Extracellular vesicle-mediated long-range communication in stressed retinal pigment epithelial cell monolayers. *Biochim Biophys Acta Mol Basis Dis.* 2018;1864(8):2610-2622. doi:10.1016/j.bbdis.2018.04.016
 142. Lazar I, Clement E, Dauvillier S, et al. Adipocyte exosomes promote melanoma aggressiveness through fatty acid oxidation: a novel mechanism linking obesity and cancer. *Cancer Res.* 2016;76(14):4051-4057. doi:10.1158/0008-5472.CAN-16-0651
 143. Clement E, Lazar I, Attané C, et al. Adipocyte extracellular vesicles carry enzymes and fatty acids that stimulate mitochondrial metabolism and remodeling in tumor cells. *EMBO j.* 2020;39(3):e102525. doi:10.15252/embj.2019102525
 144. Müller G, Schneider M, Biemer-Daub G, Wied S. Microvesicles released from rat adipocytes and harboring glycosylphosphatidylinositol-anchored proteins transfer RNA stimulating lipid synthesis. *Cell Signal.* 2011;23(7):1207-1223. doi:10.1016/j.celsig.2011.03.013
 145. Eguchi A, Lazic M, Armando AM, et al. Circulating adipocyte-derived extracellular vesicles are novel markers of metabolic stress. *J Mol Med (Berl).* 2016;94(11):1241-1253. doi:10.1007/s00109-016-1446-8
 146. Kwan HY, Chen M, Xu K, Chen B. The impact of obesity on adipocyte-derived extracellular vesicles. *Cell Mol Life Sci.* 2021; 78(23):7275-7288. doi:10.1007/s00018-021-03973-w
 147. Bandini E, Rossi T, Gallerani G, Fabbri F. Adipocytes and microRNAs crosstalk: a key tile in the mosaic of breast cancer microenvironment. *Cancers (Basel).* 2019;11(10):1451. doi:10.3390/cancers11101451
 148. Wu JF, Ho MC, Ni YH, Hsu HY, Lee PH, Chang MH. Dysregulation of liver developmental microRNA contribute to hepatic carcinogenesis. *J Formos Med Assoc.* 2020;119(6):1041-1051. doi:10.1016/j.jfma.2019.09.018
 149. Wang S, Xu M, Li X, et al. Exosomes released by hepatocarcinoma cells endow adipocytes with tumor-promoting properties. *J Hematol Oncol.* 2018;11(1):82. doi:10.1186/s13045-018-0625-1
 150. Yang WS, SriRamaratnam R, Welsch ME, et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell.* 2014;156(1-2):317-331. doi:10.1016/j.cell.2013.12.010
 151. Yagoda N, von Rechenberg M, Zaganjor E, et al. RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. *Nature.* 2007;447(7146):864-868. doi:10.1038/nature05859
 152. Yang WS, Stockwell BR. Ferroptosis: death by lipid peroxidation. *Trends Cell Biol.* 2016;26(3):165-176. doi:10.1016/j.tcb.2015.10.014

153. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060-1072. doi:10.1016/j.cell.2012.03.042
154. Yu H, Guo P, Xie X, Wang Y, Chen G. Ferroptosis, a new form of cell death, and its relationships with tumorous diseases. *J Cell Mol Med*. 2017;21(4):648-657. doi:10.1111/jcmm.13008
155. Moloney JN, Cotter TG. ROS signalling in the biology of cancer. *Semin Cell Dev Biol*. 2018;80:50-64. doi:10.1016/j.semcdb.2017.05.023
156. Fearhead HO, Vandenabeele P, Vanden BT. How do we fit ferroptosis in the family of regulated cell death? *Cell Death Differ*. 2017;24(12):1991-1998. doi:10.1038/cdd.2017.149
157. Magtanong L, Ko PJ, To M, et al. Exogenous monounsaturated fatty acids promote a ferroptosis-resistant cell state. *Cell Chem Biol*. 2019;26(3):420-432.e9. doi:10.1016/j.chembiol.2018.11.016
158. Snaebjornsson MT, Janaki-Raman S, Schulze A. Greasing the wheels of the cancer machine: the role of lipid metabolism in cancer. *Cell Metab*. 2020;31(1):62-76. doi:10.1016/j.cmet.2019.11.010
159. Bailey AP, Koster G, Guillemier C, et al. Antioxidant role for lipid droplets in a stem cell niche of drosophila. *Cell*. 2015;163(2):340-353. doi:10.1016/j.cell.2015.09.020
160. Rysman E, Brusselmans K, Scheys K, et al. De novo lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. *Cancer Res*. 2010;70(20):8117-8126. doi:10.1158/0008-5472.CAN-09-3871
161. Garg AD, Agostinis P. Cell death and immunity in cancer: from danger signals to mimicry of pathogen defense responses. *Immunol Rev*. 2017;280(1):126-148. doi:10.1111/imr.12574
162. Zhang C, Liu X, Jin S, Chen Y, Guo R. Ferroptosis in cancer therapy: a novel approach to reversing drug resistance. *Mol Cancer*. 2022;21(1):47. doi:10.1186/s12943-022-01530-y
163. Nakamura MT, Cheon Y, Li Y, Nara TY. Mechanisms of regulation of gene expression by fatty acids. *Lipids*. 2004;39(11):1077-1083. doi:10.1007/s11745-004-1333-0
164. Hopperton KE, Duncan RE, Bazinet RP, Archer MC. Fatty acid synthase plays a role in cancer metabolism beyond providing fatty acids for phospholipid synthesis or sustaining elevations in glycolytic activity. *Exp Cell Res*. 2014;320(2):302-310. doi:10.1016/j.yexcr.2013.10.016
165. Vander Heiden MG, DeBerardinis RJ. Understanding the intersections between metabolism and cancer biology. *Cell*. 2017;168(4):657-669. doi:10.1016/j.cell.2016.12.039
166. Kitahara CM, Berndt SI, de González AB, et al. Prospective investigation of body mass index, colorectal adenoma, and colorectal cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *J Clin Oncol*. 2013;31(19):2450-2459. doi:10.1200/JCO.2012.48.4691
167. Michels KB, Ekblom A. Caloric restriction and incidence of breast cancer. *Jama*. 2004;291(10):1226-1230. doi:10.1001/jama.291.10.1226
168. Masoodi M, Kuda O, Rossmel M, Flachs P, Kopecky J. Lipid signaling in adipose tissue: connecting inflammation & metabolism. *Biochim Biophys Acta*. 2015;1851(4):503-518. doi:10.1016/j.bbaliip.2014.09.023
169. Rocha DM, Bressan J, Hermsdorff HH. The role of dietary fatty acid intake in inflammatory gene expression: a critical review. *Sao Paulo Med J*. 2017;135(2):157-168. doi:10.1590/1516-3180.2016.008607072016
170. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans*. 2017;45(5):1105-1115. doi:10.1042/BST20160474
171. van der Beek CM, Dejong CHC, Troost FJ, Masclee AAM, Lenaerts K. Role of short-chain fatty acids in colonic inflammation, carcinogenesis, and mucosal protection and healing. *Nutr Rev*. 2017;75(4):286-305. doi:10.1093/nutrit/nuw067
172. Mirzaei R, Afaghi A, Babakhani S, et al. Role of microbiota-derived short-chain fatty acids in cancer development and prevention. *Biomed Pharmacother*. 2021;139:111619. doi:10.1016/j.biopha.2021.111619
173. Roopashree PG, Shetty SS, Shetty VV, Nalilu SK. Medium-chain fatty acids and breast cancer risk by receptor and pathological subtypes. *Nutrients*. 2022;14(24):5351. doi:10.3390/nu14245351
174. Hsiao WL, Pai HL, Matsui MS, Weinstein IB. Effects of specific fatty acids on cell transformation induced by an activated c-H-ras oncogene. *Oncogene*. 1990;5(3):417-421.
175. Lengyel E, Makowski L, DiGiovanni J, Kolonin MG. Cancer as a matter of fat: the crosstalk between adipose tissue and tumors. *Trends Cancer*. 2018;4(5):374-384. doi:10.1016/j.trecan.2018.03.004
176. Daquinag AC, Gao Z, Fussell C, et al. Fatty acid mobilization from adipose tissue is mediated by CD36 posttranslational modifications and intracellular trafficking. *JCI Insight*. 2021;6(17):e147057. doi:10.1172/jci.insight.147057
177. van Dijk SJ, Feskens EJ, Bos MB, et al. A saturated fatty acid-rich diet induces an obesity-linked proinflammatory gene expression profile in adipose tissue of subjects at risk of metabolic syndrome. *Am J Clin Nutr*. 2009;90(6):1656-1664. doi:10.3945/ajcn.2009.27792
178. Vaittinen M, Männistö V, Käkälä P, et al. Interorgan cross-talk between fatty acid metabolism, tissue inflammation, and FADS2 genotype in humans with obesity. *Obesity (Silver Spring)*. 2017;25(3):545-552. doi:10.1002/oby.21753
179. Dennis LK, Snetselaar LG, Smith BJ, Stewart RE, Robbins ME. Problems with the assessment of dietary fat in prostate cancer studies. *Am J Epidemiol*. 2004;160(5):436-444. doi:10.1093/aje/kwh243
180. Huang Q, Wen J, Chen G, et al. Omega-3 polyunsaturated fatty acids inhibited tumor growth via preventing the decrease of genomic DNA methylation in colorectal cancer rats. *Nutr Cancer*. 2016;68(1):113-119. doi:10.1080/01635581.2016.1115526
181. Vega OM, Abkenari S, Tong Z, Tedman A, Huerta-Yepez S. Omega-3 polyunsaturated fatty acids and lung cancer: nutrition or pharmacology? *Nutr Cancer*. 2021;73(4):541-561. doi:10.1080/01635581.2020.1761408
182. Calder PC, Kremmyda LS, Vlachava M, Noakes PS, Miles EA. Is there a role for fatty acids in early life programming of the immune system? *Proc Nutr Soc*. 2010;69(3):373-380. doi:10.1017/S0029665110001552
183. Nkondjock A, Shatenstein B, Maisonneuve P, Ghadirian P. Specific fatty acids and human colorectal cancer: an overview. *Cancer Detect Prev*. 2003;27(1):55-66. doi:10.1016/s0361-090x(02)00179-4
184. Hidaka BH, Li S, Harvey KE, et al. Omega-3 and omega-6 fatty acids in blood and breast tissue of high-risk women and association with atypical cytology. *Cancer Prev Res (Phila)*. 2015;8(5):359-364. doi:10.1158/1940-6207.CAPR-14-0351
185. Kelavkar UP, Hutzley J, Dhir R, Kim P, Allen KG, McHugh K. Prostate tumor growth and recurrence can be modulated by the omega-6: omega-3 ratio in diet: athymic mouse xenograft model simulating radical prostatectomy. *Neoplasia*. 2006;8(2):112-124. doi:10.1593/neo.05637
186. Lee HC, Liang A, Lin YH, Guo YR, Huang SY. Low dietary n-6/n-3 polyunsaturated fatty acid ratio prevents induced oral carcinoma in a hamster pouch model. *Prostaglandins Leukot Essent Fatty Acids*. 2018;136:67-75. doi:10.1016/j.plefa.2017.03.003
187. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002;13(1):3-9. doi:10.1097/00041433-200202000-00002
188. Sullivan MR, Danai LV, Lewis CA, et al. Quantification of environmental metabolites in murine cancers reveals determinants of tumor nutrient availability. *Elife*. 2019;8:e44235. doi:10.7554/eLife.44235

189. Lv M, Zhu X, Wang H, Wang F, Guan W. Roles of caloric restriction, ketogenic diet and intermittent fasting during initiation, progression and metastasis of cancer in animal models: a systematic review and meta-analysis. *PLoS ONE*. 2014;9(12):e115147. doi:[10.1371/journal.pone.0115147](https://doi.org/10.1371/journal.pone.0115147)
190. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G. Caloric restriction mimetics against age-associated disease: targets, mechanisms, and therapeutic potential. *Cell Metab*. 2019;29(3):592-610. doi:[10.1016/j.cmet.2019.01.018](https://doi.org/10.1016/j.cmet.2019.01.018)
191. Nogueira LM, Dunlap SM, Ford NA, Hursting SD. Calorie restriction and rapamycin inhibit MMTV-Wnt-1 mammary tumor growth in a mouse model of postmenopausal obesity. *Endocr Relat Cancer*. 2012;19(1):57-68. doi:[10.1530/ERC-11-0213](https://doi.org/10.1530/ERC-11-0213)
192. Le Noci V, Sommariva M, Bianchi F, et al. Local Administration of caloric restriction mimetics to promote the immune control of lung metastases. *J Immunol Res*. 2019;2019:2015892. doi:[10.1155/2019/2015892](https://doi.org/10.1155/2019/2015892)
193. Allott EH, Macias E, Sanders S, et al. Impact of carbohydrate restriction in the context of obesity on prostate tumor growth in the Hi-Myc transgenic mouse model. *Prostate Cancer Prostatic Dis*. 2017;20(2):165-171. doi:[10.1038/pcan.2016.73](https://doi.org/10.1038/pcan.2016.73)
194. Mukherjee P, Abate LE, Seyfried TN. Antiangiogenic and proapoptotic effects of dietary restriction on experimental mouse and human brain tumors. *Clin Cancer Res*. 2004;10(16):5622-5629. doi:[10.1158/1078-0432.CCR-04-0308](https://doi.org/10.1158/1078-0432.CCR-04-0308)
195. Danaei LV, Babic A, Rosenthal MH, et al. Altered exocrine function can drive adipose wasting in early pancreatic cancer. *Nature*. 2018;558(7711):600-604. doi:[10.1038/s41586-018-0235-7](https://doi.org/10.1038/s41586-018-0235-7)
196. Castejón M, Plaza A, Martínez-Romero J, Fernández-Marcos PJ, Cabo R, Díaz-Ruiz A. Energy restriction and colorectal cancer: a call for additional research. *Nutrients*. 2020;12(1):114. doi:[10.3390/nu12010114](https://doi.org/10.3390/nu12010114)
197. Lien EC, Westermark AM, Zhang Y, et al. Low glycaemic diets alter lipid metabolism to influence tumour growth. *Nature*. 2021;599(7884):302-307. doi:[10.1038/s41586-021-04049-2](https://doi.org/10.1038/s41586-021-04049-2)
198. Zhu H, Bi D, Zhang Y, et al. Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. *Signal Transduct Target Ther*. 2022;7(1):11. doi:[10.1038/s41392-021-00831-w](https://doi.org/10.1038/s41392-021-00831-w)
199. Weber DD, Aminzadeh-Gohari S, Tulipan J, Catalano L, Feichtinger RG, Kofler B. Ketogenic diet in the treatment of cancer—where do we stand? *Mol Metab*. 2020;33:102-121. doi:[10.1016/j.molmet.2019.06.026](https://doi.org/10.1016/j.molmet.2019.06.026)
200. Schulz MD, Atay C, Heringer J, et al. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature*. 2014;514(7523):508-512. doi:[10.1038/nature13398](https://doi.org/10.1038/nature13398)
201. Chang HH, Moro A, Takakura K, et al. Incidence of pancreatic cancer is dramatically increased by a high fat, high calorie diet in KrasG12D mice. *PLoS ONE*. 2017;12(9):e0184455. doi:[10.1371/journal.pone.0184455](https://doi.org/10.1371/journal.pone.0184455)
202. Labbé DP, Zadra G, Yang M, et al. High-fat diet fuels prostate cancer progression by rewiring the metabolome and amplifying the MYC program. *Nat Commun*. 2019;10(1):4358. doi:[10.1038/s41467-019-12298-z](https://doi.org/10.1038/s41467-019-12298-z)
203. Ip BC, Liu C, Smith DE, Ausman LM, Wang XD. High-refined carbohydrate and high-fat diets induce comparable hepatic tumorigenesis in male mice. *J Nutr*. 2014;144(5):647-653. doi:[10.3945/jn.113.189613](https://doi.org/10.3945/jn.113.189613)
204. Popkin BM. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. *Am J Clin Nutr*. 2006;84(2):289-298. doi:[10.1093/ajcn/84.1.289](https://doi.org/10.1093/ajcn/84.1.289)
205. Heidemann C, Schulze MB, Franco OH, van Dam RM, Mantzoros CS, Hu FB. Dietary patterns and risk of mortality from cardiovascular disease, cancer, and all causes in a prospective cohort of women. *Circulation*. 2008;118(3):230-237. doi:[10.1161/CIRCULATIONAHA.108.771881](https://doi.org/10.1161/CIRCULATIONAHA.108.771881)
206. Crowe FL, Roddam AW, Key TJ, et al. Fruit and vegetable intake and mortality from ischaemic heart disease: results from the European prospective investigation into cancer and nutrition (EPIC)-heart study. *Eur Heart J*. 2011;32(10):1235-1243. doi:[10.1093/eurheartj/ehq465](https://doi.org/10.1093/eurheartj/ehq465)
207. Esposito K, Marfella R, Ciotola M, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *Jama*. 2004;292(12):1440-1446. doi:[10.1001/jama.292.12.1440](https://doi.org/10.1001/jama.292.12.1440)
208. Toledo E, Salas-Salvadó J, Donat-Vargas C, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial [published correction appears in *JAMA Intern Med*. 2018 Dec 1;178(12):1731-1732]. *JAMA Intern Med*. 2015;175(11):1752-1760. doi:[10.1001/jamainternmed.2015.4838](https://doi.org/10.1001/jamainternmed.2015.4838)
209. Melina V, Craig W, Levin S. Position of the academy of nutrition and dietetics: vegetarian diets. *J Acad Nutr Diet*. 2016;116(12):1970-1980. doi:[10.1016/j.jand.2016.09.025](https://doi.org/10.1016/j.jand.2016.09.025)
210. Zhong VW, Van Horn L, Greenland P, et al. Associations of processed meat, unprocessed red meat, poultry, or fish intake with incident cardiovascular disease and all-cause mortality. *JAMA Intern Med*. 2020;180(4):503-512. doi:[10.1001/jamainternmed.2019.6969](https://doi.org/10.1001/jamainternmed.2019.6969)
211. Kennedy J, Alexander P, Taillie LS, Jaacks LM. Estimated effects of reductions in processed meat consumption and unprocessed red meat consumption on occurrences of type 2 diabetes, cardiovascular disease, colorectal cancer, and mortality in the USA: a microsimulation study. *Lancet Planet Health*. 2024;8(7):e441-e451. doi:[10.1016/S2542-5196\(24\)00118-9](https://doi.org/10.1016/S2542-5196(24)00118-9)
212. Bernstein AM, Song M, Zhang X, et al. Processed and unprocessed red meat and risk of colorectal cancer: analysis by tumor location and modification by time. *PLoS ONE*. 2015;10(8):e0135959. doi:[10.1371/journal.pone.0135959](https://doi.org/10.1371/journal.pone.0135959)
213. Wei M, Brandhorst S, Shelehchi M, et al. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl Med*. 2017;9(377):eaa18700. doi:[10.1126/scitranslmed.aai8700](https://doi.org/10.1126/scitranslmed.aai8700)
214. Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. *Nat Rev Cancer*. 2018;18(11):707-719. doi:[10.1038/s41568-018-0061-0](https://doi.org/10.1038/s41568-018-0061-0)
215. Cao Y. Adipocyte and lipid metabolism in cancer drug resistance. *J Clin Invest*. 2019;129(8):3006-3017. doi:[10.1172/JCI12720](https://doi.org/10.1172/JCI12720)
216. Roma-Rodrigues C, Mendes R, Baptista PV, Fernandes AR. Targeting tumor microenvironment for cancer therapy. *Int J Mol Sci*. 2019;20(4):840. doi:[10.3390/ijms20040840](https://doi.org/10.3390/ijms20040840)
217. Pasquarelli-do-Nascimento G, Machado SA, de Carvalho JMA, Magalhães KG. Obesity and adipose tissue impact on T-cell response and cancer immune checkpoint blockade therapy. *Immunother Adv*. 2022;2(1):ltac015. doi:[10.1093/immadv/ltac015](https://doi.org/10.1093/immadv/ltac015)
218. Horowitz NS, Wright AA. Impact of obesity on chemotherapy management and outcomes in women with gynecologic malignancies. *Gynecol Oncol*. 2015;138(1):201-206. doi:[10.1016/j.ygyno.2015.04.002](https://doi.org/10.1016/j.ygyno.2015.04.002)
219. Rao M, Gao C, Guo M, Law BYK, Xu Y. Effects of metformin treatment on radiotherapy efficacy in patients with cancer and diabetes: a systematic review and meta-analysis. *Cancer Manag Res*. 2018;10:4881-4890. doi:[10.2147/CMAR.S174535](https://doi.org/10.2147/CMAR.S174535)
220. Farooqi MAM, Malhotra N, Mukherjee SD, et al. Statin therapy in the treatment of active cancer: a systematic review and meta-analysis of randomized controlled trials. *PLoS ONE*. 2018;13(12):e0209486. doi:[10.1371/journal.pone.0209486](https://doi.org/10.1371/journal.pone.0209486)
221. Broadfield LA, Pane AA, Talebi A, Swinnen JV, Fendt SM. Lipid metabolism in cancer: new perspectives and emerging mechanisms.

- Dev Cell.* 2021;56(10):1363-1393. doi:[10.1016/j.devcel.2021.04.013](https://doi.org/10.1016/j.devcel.2021.04.013)
222. Steinberg GR, Carling D. AMP-activated protein kinase: the current landscape for drug development. *Nat Rev Drug Discov.* 2019;18(7):527-551. doi:[10.1038/s41573-019-0019-2](https://doi.org/10.1038/s41573-019-0019-2)
223. Svensson RU, Parker SJ, Eichner LJ, et al. Inhibition of acetyl-CoA carboxylase suppresses fatty acid synthesis and tumor growth of non-small-cell lung cancer in preclinical models. *Nat Med.* 2016;22(10):1108-1119. doi:[10.1038/nm.4181](https://doi.org/10.1038/nm.4181)
224. Li EQ, Zhao W, Zhang C, et al. Synthesis and anti-cancer activity of ND-646 and its derivatives as acetyl-CoA carboxylase 1 inhibitors. *Eur J Pharm Sci.* 2019;137:105010. doi:[10.1016/j.ejps.2019.105010](https://doi.org/10.1016/j.ejps.2019.105010)
225. Lally JSV, Ghoshal S, DePeralta DK, et al. Inhibition of acetyl-CoA carboxylase by phosphorylation or the inhibitor ND-654 suppresses lipogenesis and hepatocellular carcinoma. *Cell Metab.* 2019;29(1):174-182.e5. doi:[10.1016/j.cmet.2018.08.020](https://doi.org/10.1016/j.cmet.2018.08.020)
226. Uto Y. Recent progress in the discovery and development of stearoyl CoA desaturase inhibitors. *Chem Phys Lipids.* 2016;197:3-12. doi:[10.1016/j.chemphyslip.2015.08.018](https://doi.org/10.1016/j.chemphyslip.2015.08.018)
227. Tesfay L, Paul BT, Konstorum A, et al. Stearoyl-CoA desaturase 1 protects ovarian cancer cells from ferroptotic cell death. *Cancer Res.* 2019;79(20):5355-5366. doi:[10.1158/0008-5472.CAN-19-0369](https://doi.org/10.1158/0008-5472.CAN-19-0369)
228. Kazantzis M, Stahl A. Fatty acid transport proteins, implications in physiology and disease. *Biochim Biophys Acta.* 2012;1821(5):852-857. doi:[10.1016/j.bbali.2011.09.010](https://doi.org/10.1016/j.bbali.2011.09.010)
229. de Fraipont F, Nicholson AC, Feige JJ, Van Meir EG. Thrombospondins and tumor angiogenesis. *Trends Mol Med.* 2001;7(9):401-407. doi:[10.1016/s1471-4914\(01\)02102-5](https://doi.org/10.1016/s1471-4914(01)02102-5)
230. Herlund E, Ihlund LS, Khan O, et al. Potentiation of chemotherapeutic drugs by energy metabolism inhibitors 2-deoxyglucose and etomoxir. *Int J Cancer.* 2008;123(2):476-483. doi:[10.1002/ijc.23525](https://doi.org/10.1002/ijc.23525)
231. Holubarsch CJ, Rohrbach M, Karrasch M, et al. A double-blind randomized multicentre clinical trial to evaluate the efficacy and safety of two doses of etomoxir in comparison with placebo in patients with moderate congestive heart failure: the ERGO (etomoxir for the recovery of glucose oxidation) study. *Clin Sci (Lond).* 2007;113(4):205-212. doi:[10.1042/CS20060307](https://doi.org/10.1042/CS20060307)
232. Pacilli A, Calienni M, Margarucci S, et al. Carnitine-acyltransferase system inhibition, cancer cell death, and prevention of MYC-induced lymphomagenesis. *J Natl Cancer Inst.* 2013;105(7):489-498. doi:[10.1093/jnci/djt030](https://doi.org/10.1093/jnci/djt030)
233. Ricciardi MR, Mirabilli S, Allegretti M, et al. Targeting the leukemia cell metabolism by the CPT1a inhibition: functional preclinical effects in leukemias. *Blood.* 2015;126(16):1925-1929. doi:[10.1182/blood-2014-12-617498](https://doi.org/10.1182/blood-2014-12-617498)
234. Kuhajda FP. Fatty acid synthase and cancer: new application of an old pathway. *Cancer Res.* 2006;66(12):5977-5980. doi:[10.1158/0008-5472.CAN-05-4673](https://doi.org/10.1158/0008-5472.CAN-05-4673)
235. Ameer F, Scanduzzi L, Hasnain S, Kalbacher H, Zaidi N. De novo lipogenesis in health and disease. *Metabolism.* 2014;63(7):895-902. doi:[10.1016/j.metabol.2014.04.003](https://doi.org/10.1016/j.metabol.2014.04.003)
236. Ralph SJ, Rodríguez-Enríquez S, Neuzil J, Moreno-Sánchez R. Bioenergetic pathways in tumor mitochondria as targets for cancer therapy and the importance of the ROS-induced apoptotic trigger. *Mol Aspects Med.* 2010;31(1):29-59. doi:[10.1016/j.mam.2009.12.006](https://doi.org/10.1016/j.mam.2009.12.006)
237. Furuta E, Okuda H, Kobayashi A, Watabe K. Metabolic genes in cancer: their roles in tumor progression and clinical implications. *Biochim Biophys Acta.* 2010;1805(2):141-152. doi:[10.1016/j.bbcan.2010.01.005](https://doi.org/10.1016/j.bbcan.2010.01.005)
238. Ventura R, Mordec K, Waszczuk J, et al. Inhibition of de novo palmitate synthesis by fatty acid synthase induces apoptosis in tumor cells by remodeling cell membranes, inhibiting signaling pathways, and reprogramming gene expression. *EBioMedicine.* 2015;2(8):808-824. doi:[10.1016/j.ebiom.2015.06.020](https://doi.org/10.1016/j.ebiom.2015.06.020)
239. Tang L, He S, Yin Y, et al. Combination of nanomaterials in cell-based drug delivery systems for cancer treatment. *Pharmaceutics.* 2021;13(11):1888. doi:[10.3390/pharmaceutics13111888](https://doi.org/10.3390/pharmaceutics13111888)
240. Wen D, Wang J, Driessche GVD, et al. Adipocytes as anticancer drug delivery depot. *Phys B Condens Matter.* 2019;1(5):1203-1214. doi:[10.1016/j.matt.2019.08.007](https://doi.org/10.1016/j.matt.2019.08.007)
241. Aoki M, Kakimoto K, Goto M, Higuchi K. Novel therapeutic approach using drug-loaded adipose-derived stem cells for pancreatic cancer [retracted in: *Sci rep.* 2021 Sep 28;11(1):19626]. *Sci Rep.* 2019;9(1):17971. doi:[10.1038/s41598-019-53807-w](https://doi.org/10.1038/s41598-019-53807-w)

How to cite this article: Calabrese C, Miserocchi G, De Vita A, et al. Lipids and adipocytes involvement in tumor progression with a focus on obesity and diet. *Obesity Reviews.* 2024; 25(12):e13833. doi:[10.1111/obr.13833](https://doi.org/10.1111/obr.13833)