Seminars in Cancer Biology 93 (2023) 36–51

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Obesity-induced changes in cancer cells and their microenvironment: Mechanisms and therapeutic perspectives to manage dysregulated lipid metabolism

Miriam Lee-Rueckert [a,1], Marina Canyelles [b,c,1], Mireia Tondo [b,c], Noemi Rotllan [b,c], Petri T. Kovanen [a], Vicenta Llorente-Cortes [a,d,e,*], Joan Carles Escolà-Gil [b,c,*]

[a] Wihuri Research Institute, Helsinki, Finland
[b] Institut d'Investigacions Biomèdiques (IIB) Sant Pau, Barcelona, Spain
[c] CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain
[d] Institute of Biomedical Research of Barcelona (IIBB)-Spanish National Research Council (CSIC), Barcelona, Spain
[e] CIBERCV, Institute of Health Carlos III, 28029 Madrid, Spain

ARTICLE INFO

Keywords:
Adipocytes, cancer
Cholesterol
Fibroblasts, fatty acids
Lipids
Macrophages
Obesity
Tumor microenvironment

ABSTRACT

Obesity has been closely related to cancer progression, recurrence, metastasis, and treatment resistance. We aim to review recent progress in the knowledge on the obese macroenvironment and the generated adipose tumor microenvironment (TME) inducing lipid metabolic dysregulation and their influence on carcinogenic processes. Visceral white adipose tissue expansion during obesity exerts systemic or macroenvironmental effects on tumor initiation, growth, and invasion by promoting inflammation, hyperinsulinemia, growth-factor release, and dyslipidemia. The dynamic relationship between cancer and stromal cells of the obese adipose TME is critical for cancer cell survival and proliferation as well. Experimental evidence shows that secreted paracrine signals from cancer cells can induce lipolysis in cancer-associated adipocytes, causing them to release free fatty acids and acquire a fibroblast-like phenotype. Such adipocyte delipidation and phenotypic change is accompanied by an increased secretion of cytokines by cancer-associated adipocytes and tumor-associated macrophages in the TME. Mechanistically, the availability of adipose TME free fatty acids and tumorigenic cytokines concomitant with the activation of angiogenic processes creates an environment that favors a shift in the cancer cells toward an aggressive phenotype associated with increased invasiveness. We conclude that restoring the aberrant metabolic alterations in the host macroenvironment and in adipose TME of obese subjects would be a therapeutic option to prevent cancer development. Several dietary, lipid-based, and oral antidiabetic pharmacological therapies could potentially prevent tumorigenic processes associated with the dysregulated lipid metabolism closely linked to obesity.

Abbreviations: AMPK, AMP-activated protein kinase; ANGPTL4, angiopoietin-like 4; ATGL, adipose triglyceride lipase; ATMs, adipose tissue macrophages; BAT, brown adipose tissue; BMI, body mass index; CAAs, cancer-associated adipocytes; CAF, cancer-associated fibroblasts; CD, cluster of differentiation; CLS, crown-like structure; CPT, carnitine palmitoyltransferase; CYP27A1, sterol 27-hydroxylase; CYP7B1, oxysterol 7-hydroxylase; ECM, extracellular matrix; EPA, eicosapentaenoic acid; ER, estrogen receptor; FAO, fatty acid β-oxidation; FAS, fatty acid synthase; FATP, fatty acid transport proteins; FFA, free fatty acids; GHR, growth hormone receptor; HC, hydroxycholesterol; HIF, hypoxia-inducible factor; HSL, hormone-sensitive lipase; IGF-1, insulin growth factor-1; IL, interleukin; IDL, intermediate-density lipoproteins; LDL, low-density lipoprotein; LDLr, LDL receptor; LPA, lysophosphatidic acid; LXR, liver X receptor; MCP-1, monocyte chemoattractant protein-1; MUFA, monounsaturated fatty acids; ox-LDL, oxidized LDL; OLR1, oxidized LDL receptor 1; PI3K, phosphoinositide 3-kinase; PUFA, polyunsaturated fatty acids; PyMT, Mouse Mammary Tumor Virus-Polyoma Virus Middle T; RAGE, receptor for advanced glycation end products; sd-LDL, small dense LDL; SFA, saturated fatty acids; STAT, signal transducer and activator of transcription; TAMs, SGLT2i, sodium-glucose transport protein 2 inhibitors; SREBP1, sterol regulatory element binding protein 1tumor-associated macrophages; TME, tumor microenvironment; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; VLDL, very-low density lipoproteins; WAT, white adipose tissue.

* Correspondence to: Institutd'Investigacions Biomèdiques (IIB) Sant Pau, C/ Sant Quintí 77, 08041 Barcelona, Spain.
E-mail addresses: cllorente@santpau.cat (V. Llorente-Cortes), jescola@santpau.cat (J.C. Escolà-Gil).

[1] These authors contributed equally

https://doi.org/10.1016/j.semcancer.2023.05.002
Received 2 February 2023; Received in revised form 5 April 2023; Accepted 5 May 2023
Available online 6 May 2023

1. Introduction

The incidence of obesity has rapidly increased over the last decade, becoming a global epidemic. The last WHO report (2022) on the status of obesity reported that almost 60% of European adults are either overweight or obese, but obesity also affects nearly one in three children [1]. While the association of obesity with hypercholesterolemia, hypertension, and type 2 diabetes mellitus is well recognized, the link between obesity and cancer is relatively underestimated. In 2012, the combined effects of high body mass index (BMI) and diabetes were responsible for 5.7% of incident cancers worldwide [2]. Notably, when evaluated as independent risk factors, a high BMI was responsible for almost twice as many cancer cases as diabetes [2]. It is noteworthy to mention a recent report that showed that cancer mortality in UK subjects with type 2 diabetes to be around double that in the general population; this was particularly significant in severely obese subjects [3]. Although the burden of cancer attributable to a high BMI has been found to be greater in regions of a higher socio-demographic index, there is a significantly increasing trend in less developed countries [4]. In 2019, global esophageal cancer was the leading cause of high BMI-related disability (26.27 per 100,000), followed by colorectal (24.21 per 100,000), liver (19.24 per 100,000), breast (11.22 per 100,000) and uterine cancer (11.22 per 100,000) [4].

There are reciprocal and complex interactions between cancer cells and other surrounding nontransformed cells, as well as with other organs and systems. The tumor microenvironment (TME) is essential for cancer cell progression and metastasis, and it consists of cancer cells, immune cells, stromal cells, blood vessels, a mixture of bioactive molecules secreted by these cells, and an extracellular matrix [5]. Also, in the context of cancer pathobiology, the tumor macroenvironment has been described as the extratumoral systemic interaction of a malignant tumor with the host, with this emerging concept an extension that complements the local interaction that occurs between cancer cells and the surrounding nontransformed cells within the TME [6]. In obese individuals, malignant tumors are exposed to both local and systemic interactions promoted by an enhanced and dysfunctional adipose tissue, which has multiple abilities to promote tumorigenic processes.

Adipose tissue is a relevant endocrine organ by secreting hormones, cytokines, and other mediators that can influence the metabolism of distant organs and tissues, including malignant tumors [7]. Notably, adipose tissue expansion in obesity is associated with a metabolic syndrome characterized by critical metabolic changes, such as hyperinsulinemia and dyslipidemia, which have been related to increased cancer risk [8]. Obesity significantly modifies the TME by increasing the levels of circulating lipids and lipoproteins, which, facilitated by tumor-induced angiogenesis, enter the TME through newly formed leaky blood vessels and have significant impacts on the tumor phenotype [9].

The peritumoral adipose tissue provides multiple endocrine anomalies and secreted signaling mediators to the TME, such as proinflammatory cytokines and remodeling factors of the extracellular matrix, thereby accelerating the generation and progression of malignant tumors. In this regard, cancer-associated adipocytes (CAAs) are considered major conductors of signaling networks within the TME during body weight gain [10]. Moreover, several malignant processes occurring in cancer cells located within an adipose tissue microenvironment are regulated by a complex paracrine network that involves adipocytes, tissue-resident macrophages, fibroblasts, endothelial cells and $CD8^+$ cytotoxic T cells. To characterize the complex crosstalk between the adipose tissue and carcinomas, and due to the growing interest in the specific roles of distinct and complex components of the adipose tissue in tumor development, we have adopted the term “adipose TME”.

In this narrative review, we aim to present recent progress in the investigations on the effects of adipose tissue expansion and the generated adipose TME inducing lipid metabolic alterations in tumor cells and their influence on various carcinogenic steps in the obese setting. We finally discuss potential therapeutic interventions directed at decreasing the burden of cancer attributed to the dysregulated lipid metabolism typical of obesity. This includes nutritional and pharmacological treatments such as drugs targeting fatty acid metabolism, drugs lowering blood cholesterol levels, and hypoglycemic drugs.

2. Adipose tissue and cancer development in the obese setting

2.1. White and brown adipose tissue

In the human body, fat accumulates in two types of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT), the percentage of the latter decreasing with age. The two types of adipose tissue usually perform opposite physiological functions [11]. WAT mainly accumulates in two locations, subcutaneous and visceral fat, the expansion of the latter being the key driver of central obesity [12]. Particularly, WAT located in the visceral compartment is considered the largest endocrine organ with autocrine, paracrine, and endocrine functions [13]. Moreover, lipid peroxides secreted by the obese visceral WAT has been associated with a more protumorigenic secretome inducing expression of genes involved in the early steps of tumor promotion on the mammary gland [14]. While obesity directly relates to the expansion of WAT, BAT regulates thermogenesis. It is considered that, because BAT adipocytes are specialized for energy expenditure, they have protective roles against obesity and associated metabolic diseases [15]. Also, BAT adipocytes appear to be less susceptible to the development of inflammation than WAT adipocytes [16].

It has become clear that cancer cells respond to extratumoral and systemic metabolic stimuli associated with the host. Thus, systemic metabolic diseases, such as obesity and diabetes, are known to influence tumor development. Increased visceral adiposity in obesity is an underlying cause of metabolic disturbances leading to hypertension, hyperglycemia, and dyslipidemia—typical symptoms of metabolic syndrome. These metabolic changes further influence the local TME, increasing cancer progression in the obese patient. Thus, the overgrowth of visceral WAT has been specifically linked with cancer progression, and studies in animal models have shown that such a direct link is irrespective of diet [17,18]. In contrast, whether BAT plays a role in cancer development is less clear. A potential involvement of BAT in cancer progression has been attributed to its association with metabolic disturbances leading to cachexia, which appears in the advanced stages of cancer [19,20]. However, other studies have found that BAT may exert a beneficial effect by releasing anti-inflammatory cytokines that could regulate the TME, which in turn would improve cancer prognosis by hindering the progression of different types of malignant tumors [21]. Because of all the above-mentioned uncertainties regarding the mechanistic and prognostic role of BAT in cancer development, in the next sections, we will mainly refer to the tumorigenic role of WAT adipocytes present in the intra-abdominal visceral depot, which we will simply refer to as “adipose tissue.”

2.2. Metabolic syndrome and its role in cancer development

Although not all types of malignant tumors are surrounded by CAAs, carcinomas are fueled by direct exposure to proximal adipocytes—as occurs in invasive carcinomas in the reproductive and digestive organs—which initiates a paracrine and cell-to-cell contact-dependent signaling crosstalk [22]. The cell population in the adipose tissue is heterogeneous and, besides the adipocytes, other cell types are present, including macrophages, stem cells, preadipocytes, fibroblasts, neutrophils, lymphocytes, mast cells, and capillary endothelial cells [23]. The metabolic crosstalk that occurs between the adipocytes and the network of non-adipocyte cells, especially macrophages, strongly regulates various functions of the adipose tissue. Altogether, the adipocytes and non-adipocyte cells of the adipose tissue secrete a wide variety of cell-signaling molecules and metabolic mediators called adipokines. Of

note, while the ovaries are the major source of estrogen in premenopausal women, adipose tissue displays a high estrogenic enzyme activity and contains considerable local estrogen concentrations [24].

Despite the adiposity degree generally being measured based on "fatness" (i.e., BMI or waist circumference), changes in the quality of the adipose tissue in obese individuals are important drivers of metabolic disturbances related to cancer development. The long-term accumulation of cellular lipids in adipocytes is associated with expanded and dysfunctional adipose tissue, which plays an important role in the development of metabolic syndrome. When a malignant tumor has developed in such an obese setting, several interactions with the tumor will be mediated by extratumoral components released to the circulation by the inflamed adipose tissue. We have to note that, although increased adiposity per se induces various disturbances in the profile of circulating lipids associated with cancer progression, they occur in parallel to other non-lipid metabolic disorders typical of the metabolic syndrome, such as hyperinsulinemia, hyperleptinemia, and inflammation, which also are tumorigenic.

As adipocytes increase in quantity and size, they start to secrete inflammatory adipokines and cytokines, including leptin, tumor necrosis factor-α, interleukin (IL) 6, and monocyte chemoattractant protein-1 (MCP-1), which are known to induce both systemic inflammation and inflammation in the adipose tissue and the levels of which are elevated in colon cancer [25]. It is considered that the key metabolic modifications in dysfunctional adipocytes favoring cancer development include their insulin resistance, an increased expression of aromatase (an enzyme that converts androgens to estrogens), and changes in the adipocyte-derived secretome [7,14]. Jointly, these combined factors can modify the tissue microenvironment, changing the functionality of other neighboring cells and leading them to potentially become cancerous cells. Furthermore, increased adiposity associated with both local inflammation of the adipose tissue and systemic inflammation has been reported to increase the risk of tumor growth through mechanisms including abnormal cell signaling derived from a chronic inflammatory state, an enhanced cell migratory capacity associated with the epithelial-mesenchymal transition (EMT), tumor-related fibrosis, angiogenesis, and genomic instability [26].

Hyperinsulinemia can precede and cause obesity by regulating adipocyte lipogenic and lipolytic pathways [27]. Early studies in rodent models reported that mere insulin administration induced the growth of mammary tumors and colonic abnormalities, notably the formation of aberrant crypts in the colon [28,29]. Further clinical and epidemiological studies have shown that hyperinsulinemia in humans is associated with increased cancer morbidity and mortality independent of diabetes, obesity, and metabolic syndrome [30]. Prolonged hyperinsulinemia and insulin resistance in overweight and obese individuals have been found to upregulate the growth hormone receptor (GHR), enhance GHR signaling, increase the production of hepatic insulin growth factor-1 (IGF-1), and increasing the availability of estrogens and androgens [31]. Both insulin and IGF-1 stimulate cell division and promote the development of pancreatic, colorectal, liver, postmenopausal breast, and endometrial cancers [32]. The insulin receptor has two isoforms, where INSR-A is the one predominantly upregulated with cancer progression [33,34]. An increased INSR-A/INSR-B ratio has been reported in breast, prostate, endometrial, colon and lung cancers. The main transcription factors involved in this increase ratio are AT-Hook1, specificity protein 1, and tumor protein p53 [35,36].

By upregulating the estrogen and androgen levels, increased insulin levels can stimulate the growth of hormone-dependent malignant tumors, such as in the breast, prostate, and endometrium. In contrast, body changes that occur upon weight loss may reduce cancer risk by decreasing circulating levels of insulin and the steroid hormones estrogens and androgens. In particular, estrogens, which constitute a significant type of metabolic mediators released by lipid-laden adipocytes, are capable of inducing accelerated cell division in cells that are estrogen-sensitive, such as the breast cells. This fact partially discloses an association between the high circulating estrogen levels often found in obese postmenopausal women with breast cancer [37]. Furthermore, there is growing evidence that weight loss might reduce the risk of some types of cancer, such as breast cancer in postmenopausal women. Interestingly, high estrogen levels are also found in obese men [38]. Men with the highest BMI have been found to have a 35% greater risk of breast cancer compared to men with the lowest BMI. The elevated risk observed in men with a high BMI and who often have excess breast tissue and elevated estrogen levels appears to be similar to the pattern for breast-cancer risk in postmenopausal women [39].

The enhanced secretion of leptin and decreased secretion of adiponectin from the adipose tissue of obese subjects are considered to be independent risk factors for the progression of esophageal adenocarcinoma and breast cancer [40,41]. Obesity also triggers other intracellular pathways that upregulate cyclooxygenase-2, signal transducer and activator of transcription (STAT)− 3, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) oncogenic pathways, which increase inflammation, cellular proliferation, and antiapoptotic proteins [42,43].

Another central feature of obesity, the dyslipidemia, is mainly caused by an increased flux of visceral adipocyte-derived free fatty acids (FFA) to the liver, thereby leading to the hepatic accumulation of triglycerides and the enhanced synthesis and secretion of very-low-density lipoproteins (VLDL) [44]. Furthermore, the lipoprotein lipase-mediated lipolysis of VLDL is impaired in obese individuals with insulin resistance, thereby contributing to the accumulation of triglyceride-containing lipoproteins in the blood. Normally, the VLDL particles shrink in diameter during lipolysis, thus forming intermediate-density lipoproteins (IDL). The triglycerides within the IDL are hydrolyzed by hepatic lipase, which results in the formation of the increased concentrations of small dense low-density lipoprotein (sd-LDL) particles found in obese subjects [44]. The enhanced oxidative stress particularly damages the circulating sd-LDL particles in obese subjects, forming oxidized LDL (ox-LDL) particles that have been closely linked to abdominal obesity [45]. Moreover, the plasma levels of ox-LDL were significantly increased in obese colon cancer patients with advanced grading [46]. These observations suggest that an enhanced availability of these circulating lipoproteins may occur in the obese adipose TME, with the potential to influence cancer cell behavior (see Section 3.2). Notably, the obesogenic diets induce the accumulation of saturated fats within the brain which drive the aggressively of glioblastoma in experimental mice [47], disclosing a potential pathway by which the obese systemic macroenvironment promotes the most aggressive malignant primary brain tumor.

The main metabolic features associating obesity and/or metabolic syndrome with specific cancer types are shown in Table 1. The characteristic features of the obese macroenvironment and their influence in cancer development are schematized in Fig. 1.

3. Lipid metabolism in cancer cells in the obese setting

3.1. Intrinsic regulation of lipid metabolism in cancer cells

Although the enhancement in the aerobic glycolytic pathway is the main metabolic alteration in cancer cells [48], these rapidly dividing cells use different lipid types to sustain their energy demands and membrane formation [49]. The lipid abundance in cancer cells is regulated by three central pathways: lipid uptake, *de novo* lipogenesis, and fatty acid β-oxidation (FAO).

Both cholesterol and FFA are acquired by cancer cells from extracellular sources, including the uptake of LDL-cholesterol via LDL receptors (LDLr) and FFA uptake via fatty acid transport proteins (FATPs) and the cluster of differentiation (CD) 36, a multifunctional membrane-pattern recognition receptor capable of delivering biologically active lipids to cells, including modified LDL particles and fatty acids [50–52]. Cancer cells also reactivate the intrinsic lipid supply by enhancing *de novo* fatty acid and cholesterol synthesis. Indeed, fatty acid synthesis can

Table 1
Association of obesity and/or metabolic syndrome with specific types of cancer.

Key component	Mechanism	Type of Cancer	References
WAT expansion	Visceral WAT secretes lipid peroxides	Breast	[14]
	Visceral WAT is expanded by either hypertrophy or hyperplasia, generating CLS and inducing systemic inflammation via secretion of TNF, IL-6 and MCP-1	Breast and colon	[25,26]
	Enhanced visceral WAT-mediated estrogen secretion	Breast	[37]
	Enhanced visceral WAT-mediated leptin secretion	Breast, colon, and esophageal	[40,41]
Hyperinsulinemia	Insulin receptor signaling interacts with master regulators of cancer	Pancreatic, breast, colorectal, prostate, endometrial, liver, and ovarian	[30]
	Prolonged hyperinsulinemia enhances the growth hormone receptor signaling and increases IGF-1 production	Prostate, breast, colorectal, and lung	[31,32]
Dyslipidemia	Higher levels of ox-LDL	Colon	[46]
Extracellular matrix	Increased tissue stiffness in the adipose TME, promoting retention of lipoproteins and TAMs	Breast, colorectal, prostate, and melanoma	[66,67]

Cancer-inducing mechanisms attributed to the obese setting in various tumor body locations. CLS, crown-like structures; IGF-1, insulin growth factor-1; IL-6, interleukine-6; MCP-1, monocyte chemoattractant protein-1; ox-LDL, oxidized-LDL; TAMs, tumor-associated macrophages; TME, tumor microenvironment; TNF, tumor necrosis factor; WAT, white adipose tissue.

use a variety of substrates to generate acetyl-CoA (i.e., glucose, glutamine, citrate, or acetate) to generate saturated fatty acids [50]. The predominance of saturated fatty acids is particularly higher in the membranes of lipogenic tumors, including the breast, colorectum, prostate, bladder, ovary, esophagus, stomach, lung, tongue, oral cavity, head and neck, thyroid, and endometrium [53]. This is concomitant with higher membrane sphingomyelin and cholesterol content and is particularly relevant in chemotherapy-resistant ovarian and leukemia cancer cells [54,55]. The proto-oncogene MYC is coordinated with the main lipogenic transcription factor sterol regulatory element binding protein 1 (SREBP1) that regulates fatty acid synthesis in lymphoblastic leukemia, renal, hepatocellular and lung cancer cells [56]. The mobilization of FFA from triglycerides stored in lipid droplets is catalyzed by different lipases and lipophagy, contributing to the cellular fatty acid pool in cancer cells [50]. Intracellular fatty acids are also used for phosphoglyceride synthesis, with monounsaturated and saturated fatty acid chains being characteristics of cancer cell lines and tumor specimens [57]. The release of fatty acids from membrane lipids by the action of phospholipase D results in the formation of the signaling molecule lysophosphatidic acid (LPA), thereby activating multiple oncogenic signaling pathways in ovarian, pancreatic, and breast cancer cells [58]. *De novo* cholesterol synthesis is a complex process by which cholesterol is generated from acetyl-CoA via a cascade of enzymatic reactions, also called the mevalonate pathway. Cholesterol synthesis is upregulated in estrogen receptor (ER)-negative breast cancer and pancreatic adenocarcinoma cells [59,60]. Furthermore, cholesterol accumulation in the mitochondria may disrupt mitochondrial membrane fluidity, which in turn impairs mitochondrial outer membrane permeabilization and apoptotic processes in cancer cells [61]. The mevalonate pathway also generates the intermediate isoprenoid farnesyl-pyrophosphate, which can prenylate small G proteins required for cell growth and migration [62]. After being synthesized in cancer cells, long-chain saturated fatty acids are transported into the mitochondria by carnitine palmitoyltransferase (CPT) I to generate acetyl-CoA, which enters the citric acid cycle, thereby providing cellular energy. The complete process is called FAO and is considered to be essential for cancer cell survival [63].

3.2. *Exogenous lipid supply to cancer cells*

Physicochemical differences are present between lean and obese ECM [64]. It is nowadays considered that the extracellular matrix (ECM) of the adipose tissue links obesity with cancer through the integration of hormonal, inflammatory, biomechanical, and lipidic control of tumor progression [64]. The ECM of obese mammary tissue is composed of increased levels of profibrotic components, such as collagen I and VI, fibronectin, and hyaluronic acid that form stiffened and more aligned collagen fibers that induce mechanosignaling changes that influence tumor growth, invasion, and response to therapy [65]. Breast cancer cells interacting with a stiff matrix have shown the activation of the transcription factor TWIST1, which promotes the EMT, a highly invasive and metastatic tumor phenotype [66]. The expression of biglycan, a class I small leucine-rich proteoglycan, is dysregulated in metabolic conditions such as obesity, and the overexpression of this proteoglycan has been reported to contribute to tumor growth, invasion, and metastasis [67]. Furthermore, heparan, chondroitin, and keratin sulfate proteoglycans modulate different metabolic aspects, such as the uptake of microvesicles and lipoproteins, the retention of immune cells, and low-grade inflammation processes, all of which are crucial in the initiation and progression of obesity-associated cancer [68].

ECM remodeling of the obese adipose tissue also has an important role in cancer progression [69]. The low-grade chronic inflammation characteristic of obesity promotes the infiltration of macrophages and other immune cells in the adipose tissue. Notably, within the obese adipose tissue microenvironment, abundant macrophages surround the hypoxic, necrotic, and already-dead adipocytes, forming characteristic crown-like structures (CLSs), a key feature of adipose tissue inflammation (Fig. 1 and [70]). Besides the presence of inflammatory cells, there is an increased population of myofibroblasts in obese adipose tissue. These myofibroblasts, together with the adipocytes, promote fibrotic ECM production, deposition, and remodeling. The stiffness of the adipose tissue ECM stimulates mechanosignaling transduction to local cancer cells, mediating cell proliferation and inflammation in a paracrine manner (Table 1). Altogether, the changes in the myofibroblasts, adipocytes, and macrophages within the obese mammary gland create a niche for cancer cell growth and migration [64].

The higher availability of FFA together with the hypoxic and acidic conditions in the TME promotes the uptake of FFA by cancer cells through changes in mitochondrial and histone acetylation, suggesting that the reprogramming of lipid metabolism could also be relevant in the obese adipose TME (see Sections 3.3 and 3.4) [71]. An enhanced lipid uptake through LDLr and CD36/FATP contributes to increased ratios of monounsaturated fatty acids (MUFA)/saturated fatty acids and MUFA/polyunsaturated fatty acids (PUFA) in cancer-cell membranes [50]. These alterations result in the reduced accumulation of lipid peroxides in PUFA which are required for the destruction of cells [72]. Notably, lipoprotein lipase and CD36 expression levels were found to be upregulated in lymph-node metastasis-positive samples of obese subjects with gastric cancer concomitant with the accumulation of lipid droplets, thereby reflecting the importance of the triglyceride lipolysis and the exogenous supply of FFA in obesity-related metastatic processes [73]. Many malignant tumors, including breast, prostate, ovarian, and pancreatic tumors, colocalize with CAA at various stages of the disease, thereby constituting a relevant source of FFA for tumor cells [74]. This accumulation of adipocyte-derived fatty acids in cancer cells is facilitated by increased levels of a range of fatty acid uptake-related proteins

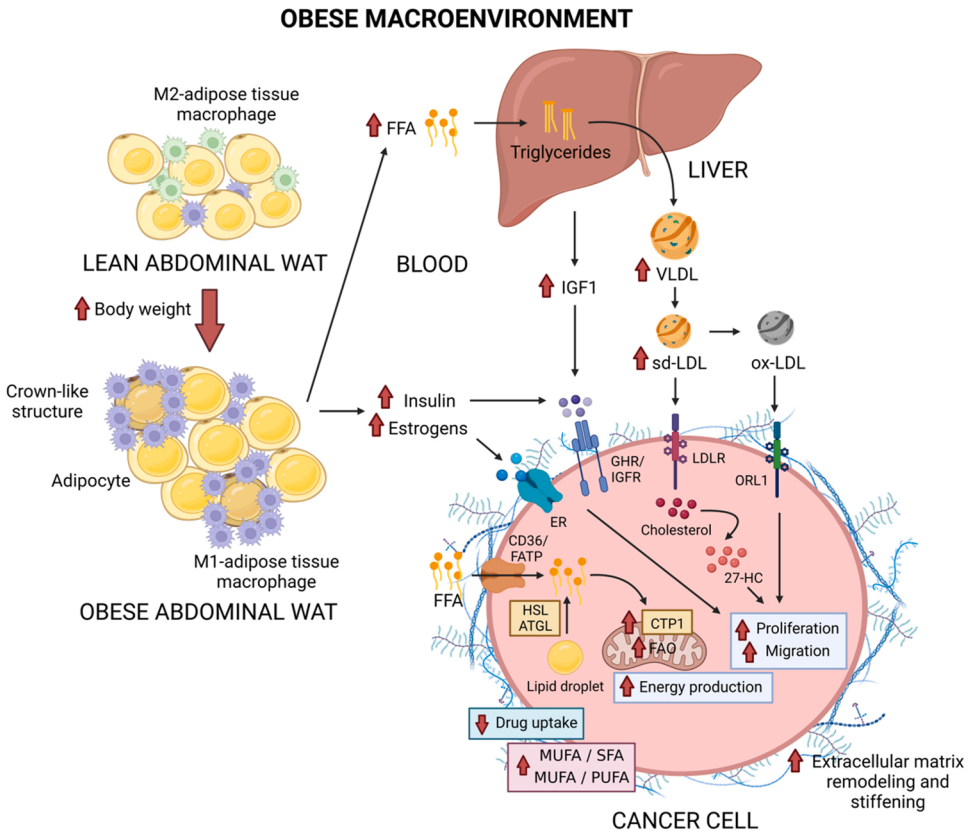

Fig. 1. The obese macroenvironment affects the exogenous lipid supply and intracellular lipid metabolism of cancer cells. Lean white adipose tissue (WAT) exhibits resident M2-adipose tissue macrophages involved in support a metabolic homeostasis. Body weight gain is associated with an expanded visceral WAT characterized by an increase in the number and size of adipocytes, which leads to damage and the necrosis of these cells. Necrotic adipocytes become encircled by M1-adipose tissue macrophages, forming crown-like structure. Metabolic syndrome, typical of obesity, is associated with hyperinsulinemia, the development of chronic inflammation, and an enhanced flux of circulating free fatty acids (FFA) to the liver, which induces a higher accumulation of triglycerides and increased hepatic synthesis of large very low-density lipoproteins (VLDL) and their conversion into small dense low-density lipoprotein (sd-LDL). Excess oxidative stress induces the formation of oxidized LDL (ox-LDL) particles that bind to lectin-like oxidized LDL receptor 1 (OLR1), resulting in cell proliferation and migration. An abnormal accumulation of extracellular matrix proteoglycans, particularly biglycan, and alterations in the extracellular matrix composition and density in the setting of obesity promote the retention of LDL and its uptake by cancer cells via LDL receptors (LDLr). Extracellular fatty acid uptake via fatty acid transport proteins (FATPs) and the cluster of differentiation (CD) 36 and fatty acids mobilized from lipid droplets are transported into the mitochondria for carnitine palmitoyltransferase I (CPT1)-mediated fatty acid oxidation (FAO), thereby supporting cellular energy production and regulation of redox homeostasis. The higher relative content of monounsaturated fatty acids (MUFA) versus saturated fatty acids (SFA) and polyunsaturated fatty acids (PUFA) in membrane lipids reduces membrane fluidity and drug uptake. Furthermore, the conversion of LDL-derived cholesterol into 27-hydroxycholesterol (27-HC) induces multiple tumorigenic pathways. Prolonged hyperinsulinemia upregulates the growth hormone receptor (GHR), signaling the production of hepatic insulin growth factor-1 (IGF-1), thereby stimulating cancer cell proliferation and migration. The enhanced production of estrogen in adipose tissue during obesity may also aggravate these carcinogenic processes via estrogen receptor (ER). ATGL, adipose triglyceride lipase; CD, cluster of differentiation; CLS, crown-like structure; CPT, carnitine palmitoyltransferase; ER, estrogen receptor; FAO, fatty acid β-oxidation; FATP, fatty acid transport proteins; FFA, free fatty acids; GHR, growth hormone receptor; HC, hydroxycholesterol; HSL, hormone-sensitive lipase; IGF-1, insulin growth factor-1; LDL, low-density lipoprotein; LDLr, LDL receptor; MUFA, monounsaturated fatty acids; ox-LDL, oxidized LDL; OLR1, oxidized LDL receptor 1; PUFA, polyunsaturated fatty acids; sd-LDL, small dense LDL; SFA, saturated fatty acids; VLDL, very-low density lipoproteins; WAT, white adipose tissue.

that are required for adipocyte growth, as displayed with the protumoral actions of fatty acid-binding protein 5 in breast cancer cells [75]. Therefore, adipocyte FFA transfer to cancer cells stimulates intracellular fatty acid metabolism and results in changes in the membrane composition that promote chemoresistance in the setting of obesity [76].

As mentioned above, ox-LDL levels are positively associated with an increased risk of cancer in obesity and, moreover, ox-LDL leads to increased cancer cell proliferation and migration via CD36 and lectin-like oxidized LDL receptor 1 (OLR1) (Table 1, Fig. 1 and [51]). Intracellular lipid droplets are crucial for tumor aggressiveness, chemoresistance, and metastasis, and cholesteryl ester-enriched lipid droplets are strongly induced by aggregated LDL in pancreatic cancer cells, supporting exacerbated cancer cell growth [77]. The overexpression of LDL receptor-related protein 1, which plays a crucial role in the uptake of aggregated LDL [78], has been associated with invasion and poor prognosis in pancreatic ductal carcinoma [79]. However, whether aggregated LDL is a driver of tumorigenic processes in the obese setting is unknown. Finally, the VLDL receptor is also a key receptor for exogenous lipid acquisition in breast cancer cells [80], but its link with obesity has not yet been disclosed.

Several epidemiological studies have shown an inverse correlation between high-density lipoproteins (HDL) and cancer risk [81]. Of note, low levels of HDL characterize the dyslipidemia of obesity [44], thus compromising key HDL antitumoral functions—e.g. their antioxidant activity reducing oxidative stress and the formation of ox-LDL [51] and the HDL-mediated cholesterol removal from cancer cells [82], which may favor tumor development. However, HDL might provide cholesterol and act as a signaling molecule via scavenger receptor type BI, which is overexpressed in some types of cancer cells [81], resulting in a increased cholesterol uptake and elevated signal transduction for cellular proliferation and tumor formation [51]. Although the interplay between the HDL pro- and anti-tumorigenic functions and cancer cells in obese individuals has not been fully disclosed, some trials using synthetic HDL and HDL-mimetic particles in cancer therapy suggest that increasing HDL levels along with consequent improvement in the function of HDL in the TME and the induction of intracellular cholesterol efflux may be a promising tool in cancer therapy, particularly the treatment of obese cancer patient [83–85].

3.3. Adipose tumor microenvironment tends to be hypoxic

Tumor cells can modify and adapt lipid metabolism to fit their own

benefit and overcome adverse conditions. This adaptation can come from genetic and epigenetic alterations and/or be driven by adverse conditions in the adipose TME, such as hypoxia and acidity generated by an enhanced glycolytic metabolism [86,87]. Furthermore, the increase in the hyaluronic content during fibrotic ECM remodeling elevates the osmotic pressure within the interstitial space, thereby impairing the blood supply and further promoting hypoxia in the TME [88]. The exposure of tumor-associated macrophages (TAMs), vascular cells, and cancer-associated fibroblasts (CAF) to different lipids and growth factors is critical in promoting TAM phenotype changes, angiogenesis, and CAF expansion, which regulate different steps of tumor formation, progression, metastasis, and drug resistance [89]. There is significant heterogeneity within the TME, mainly as a consequence of the variation in the flow of blood-derived nutrients and oxygen into the various TMEs. Therefore, oxygen and lipid concentrations may form steep gradients, resulting in zones heavily depleted of these circulating-derived factors, particularly in those distant from the vasculature where the extracellular fluid also turns acidic, and also may prevent the penetration of and response to nano-sized drug delivery systems for tumor treatment [90–92].

Under hypoxic conditions, the contribution of glucose-derived carbon to maintain the tricarboxylic acid cycle is compromised and, thus, *de novo* lipogenesis is essential to promote cell survival [93]. For example, hypoxia shifts glutamine metabolism from oxidation to reductive carboxylation in cancer cells via hypoxia-inducible factor (HIF) 1α activation, thereby generating acetyl CoA for *de novo* fatty acid synthesis [94]. The saturated fatty acids are elongated and desaturated by fatty acid elongases and stearoyl-CoA desaturase, respectively, to form a pool of non-essential fatty acids, including monounsaturated fatty acids [95]. The importance of desaturation is critical for the survival of cancer cells since the relative abundance of monounsaturated fatty acids in the membranes prevents the induction of endoplasmic reticulum stress and mitochondrial dysfunction under oxygen-deprived and nutrient-deprived conditions [95]. Furthermore, low perfusion in some tumor zones activates the receptor-mediated scavenging of albumin and macropinocytotic consumption of TME components, thereby providing lipids for cancer cell proliferation [96].

It is well known that there are reciprocal and deregulated interactions between cancer and stromal cells, which chronically modify the obese adipose TME. These interactions can also affect the lipid profile of cancer cells, as is schematized in Fig. 2. The contributions of cancer-associated host cells to tumorigenic mechanisms in the different

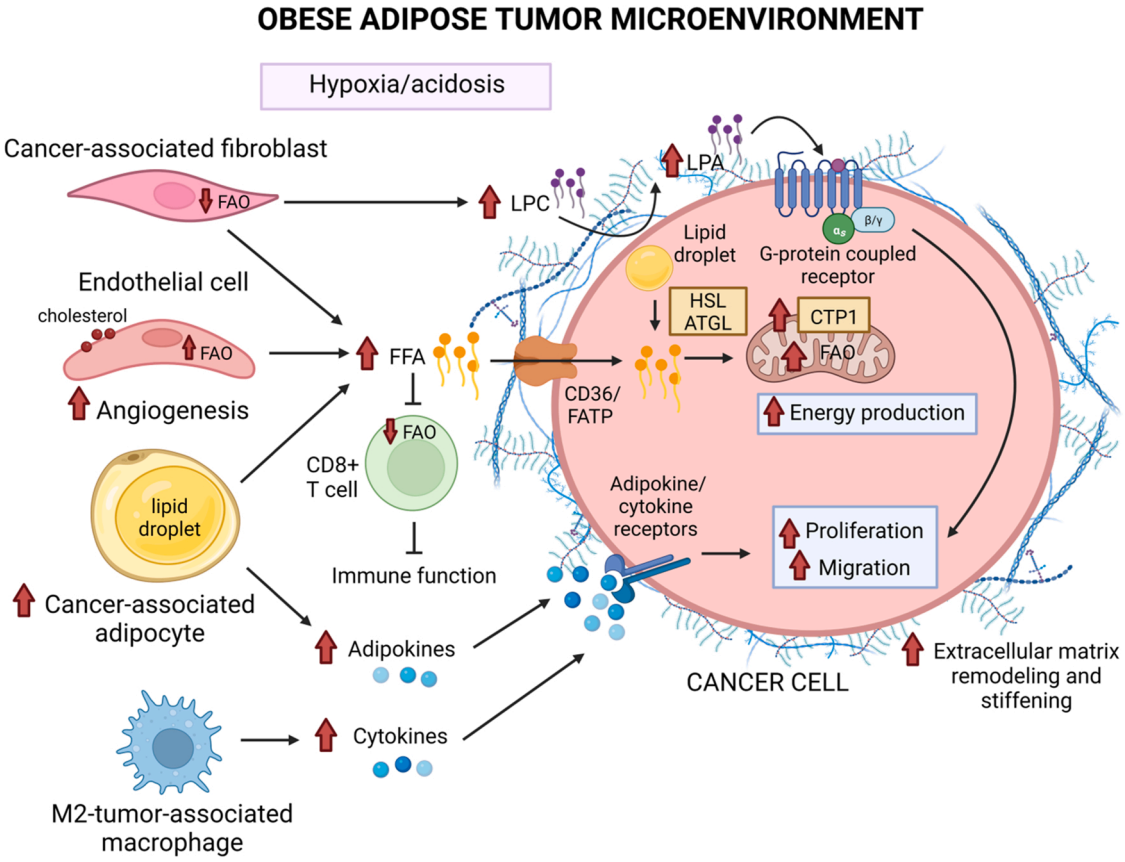

Fig. 2. Lipid metabolic alterations in the obese adipose tumor microenvironment. A key feature of the obese adipose tumor microenvironment is acidosis caused by hypoxia. Cancer-associated adipocytes, cancer-associated fibroblasts, and endothelial cells within the obese tumor microenvironment constitute major sources of free fatty acids (FFA) for local cancer cells that induce carnitine palmitoyltransferase I (CPT1)-mediated fatty acid oxidation (FAO) and lipid droplet fatty acid mobilization via adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). These changes in the fatty acid metabolism of a tumor are essential for cancer cell energy production. Cancer-associated fibroblasts can release lysophosphatidylcholines (LPC) to support cancer cell membrane lipid synthesis, thereby facilitating the production of lysophosphatidic acid (LPA) and leading to cell proliferation and migration. Accelerated fatty acid uptake in cancer cells reprograms fatty acid metabolism in tumor-infiltrating $CD8^+$ T cells, thus impairing their immune function. The expansion and activation of cancer-associated adipocytes during obesity secretes multiple pro-angiogenic factors. Angiogenic processes in endothelial cells are also promoted by FAO, fatty acid synthesis, and higher cholesterol content of endothelial cell membranes. Cancer cells scavenge membrane cholesterol from tumor-associated macrophages and induce their reprogramming toward the tumor-promoting M2 phenotype. Inflammatory cytokines and adipokines released by M2- tumor-associated macrophages and by cancer-associated adipocytes can aggravate the proliferation and invasion processes of tumors through interaction with their specific receptors in cancer cells. ATGL, adipose triglyceride lipase; CD, cluster of differentiation; CPT, carnitine palmitoyltransferase; FAO, fatty acid β-oxidation; FAS, fatty acid synthase; FATP, fatty acid transport proteins; FFA, free fatty acids; HSL, hormone-sensitive lipase; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholines.

obesity-related cancer cells are described in detail in the following sections and summarized in Table 2.

3.4. Obesity and intracellular lipid metabolism in cancer cells

As referred to above, CAAs located in the adipose TME may offer an accessible reservoir of lipids for the high-energy requirements of cancer cells [97]. There is direct evidence that the increased bioavailability of CAA-derived FFA affects intracellular cancer cell metabolism (Table 2). Indeed, primary human adipocytes promote not only the homing, migration, and invasion of ovarian cancer cells but also the direct transfer of FFA to ovarian cancer cells and the enhancement of the FAO via upregulating CPT1 and acyl-CoA oxidase 1 [98]. Interestingly, ovarian cancer cells also induced lipolysis in adipocytes by inducing the phosphorylation of hormone-sensitive lipase and perilipin A, suggesting a mutual adaptation that allows cancer cells to thrive on adipocyte-derived FFA [98]. The enhanced FAO also contributes to the EMT in breast cancer cells through their contact with adipocytes [99]. This process is also fueled by adipose triglyceride lipase- and hormone-sensitive lipase lipolytic-dependent pathways, which ensure the release of FFA from the lipid droplets and so enable their availability for FAO [75,99]. However, whether these co-culture models are physiologically representative of an obese setting is questionable. In this context, the most remarkable findings are that adipocytes obtained from lipid-loaded human cultured lines or primary adipocytes from obese mice also transferred FFA to breast cancer and melanoma cells and enhanced FAO and lipid storage, leading to higher proliferation and migration rates when compared with the effects mediated by lean adipocytes [100,101]. Furthermore, monoacylglycerol lipase seems to be another critical enzyme regulating the release of fatty acids from neutral lipid stores in aggressive melanoma, ovarian, and breast cancer cells [102]. Consistent with these findings, exogenous sources of saturated fatty acids from obesogenic diets also contribute to malignancy in these cancers in vivo [102].

27-hydroxycholesterol (27-HC) is closely associated with circulating cholesterol levels and plays a key role in cancer development in the setting of obesity (Fig. 1 and [103]. This cholesterol metabolite is intracellularly generated by the action of sterol 27-hydroxylase (CYP27A1) and catabolized by oxysterol 7-hydroxylase (CYP7B1), forming bile acids [104]. 27-HC increased spontaneous breast cancer tumor growth in an ER-dependent manner in the mouse mammary tumor virus-polyoma virus middle T antigen (PyMT) transgenic mice fed an obesogenic diet [103]. Furthermore, a lack of the CYP27A1 enzyme attenuated the effects of this obesogenic diet on the growth of breast cancer tumors in hypercholesterolemic mice [103]. 27-HC also accelerated cancer cell metastasis to the lungs in these mice, an effect that implicated liver X receptor (LXR) activation [103]. The pro-metastatic actions of 27-HC also required both polymorphonuclear-neutrophils and γδ-T cells together with an immune depletion of $CD8^+$ T cells in obese and hypercholesterolemic mice, although the precise signaling events involved in this process are not yet known [105]. It should be noted that 27-HC administration also increased xenografted ER-positive breast cancer tumor growth in non-obese ovariectomized female immunodeficient mice [106]. In the referred report, 27-HC was found to be increased in ER+ human breast cancer tissues in close association with CYP7B1 downregulation, whereas CYP27A1 remained unchanged [106]. Moreover, another report demonstrated that 27-HC induces angiogenesis by promoting the expression of vascular endothelial growth factor (VEGF) in an ER-dependent manner in ER-positive breast cancer cells or by activating STAT3 in an ER-independent manner [107]. 27-HC also induces the EMT by downregulating E-cadherin and β-catenin expression [108] as well as by upregulating the phosphorylation of STAT3, which was found to promote matrix metalloproteinase-9 expression [109]. Overall, these findings clearly indicate that the conversion of cholesterol to 27-HC could also be a key factor in explaining the evidence that links 27-HC with other obesity-related cancers, such as prostate [110], endometrial [111], thyroid [112], and ovarian [113] malignancies. Of note, 25-HC is also catabolized by CYP7B1 and induces the recruitment of protumoral monocytes in glioblastoma tumors [114]. Furthermore, 25-HC also stimulates growth in breast and ovarian cancer cells in an ER-dependent manner [115].

4. Cancer-associated host cells in the obese setting

4.1. Adipose tissue macrophages, tumor-associated macrophages, and tumor growth

Macrophages are highly plastic cells that can be polarized in vitro towards a classical (M1 or pro-inflammatory) or alternative (M2 or anti-inflammatory) activation state [116]. However, variable in vivo inflammatory conditions in the macrophage microenvironment can lead to a vast array of activation phenotypes with distinct metabolic profiles and can even produce phenotype shifts as a mechanism towards maintaining metabolic homeostasis, as occurs during the onset of obesity and cancer [117]. Whereas lean adipose tissue is enriched with permanently resident immune cells— which are largely anti-inflammatory and promote normal metabolic homeostasis—in obese adipose tissue, proinflammatory immune cells are progressively recruited, which drives the development of insulin resistance and systemic metabolic dysregulation [118]. Whereas in lean adipose tissue, the adipose tissue macrophages (ATMs) are interstitially spaced, they form clusters in the obese setting (Fig. 1). The levels of MCP-1 in adipose tissue and plasma were found to be increased in genetically obese diabetic leptin-receptor-deficient mice and in wild-type mice fed a high-fat diet [119]. Thus, it follows that ATMs must be continually recruited in obese adipose tissue under the influence of MCP-1, a conclusion that is consistent with the data showing that macrophages make up to 40% of all adipose tissue cells in obese mice compared to 10% in lean mice [120].

The ATM content is higher in visceral than in subcutaneous adipose tissue, which supports the concept that visceral fat plays a more

Table 2
Contribution of cancer-associated host cells in the TME to tumorigenic mechanisms in obesity-related cancer.

Host Cells	Mechanisms	Type of Cancer	References
Cancer-associated adipocytes	Transfer lipids, mainly FFAs, to cancer cells	Breast, colorectal, prostate, ovarian, and pancreatic	[74,98]
	Secretion of angiogenic and tumorigenic adipokines	Breast and ovarian	[74,164]
Tumor-associated macrophages	Adopt protumoral M2-like immunosuppressive phenotype that secretes tumorigenic cytokines	Breast	[137]
Cancer-associated fibroblasts	Transfer lipids to cancer cells, mainly FFAs and lysophosphatidylcholines	Breast, colorectal and pancreatic	[145,146, 148]
Endothelial cells	Transfer lipids to cancer cells, mainly FFAs	Breast	[163]
$CD8^+$ T cells	Impaired $CD8^+$ T cell activation via fatty acid uptake	Colorectal, breast and melanoma	[172]

Tumorigenic mechanisms attributed to cancer-associated host cells in the tumor microenvironment. CD, cluster of differentiation; FFA, free fatty acids; TME, tumor microenvironment.

prominent role in insulin resistance [121]. Indeed, the presence of CLSs in WAT was found to correlate with metabolic dysfunction even in women with normal BMI [122]. Moreover, the presence of CLSs was associated with elevated levels of aromatase and an increased risk of breast cancer in women with a history of benign breast disease [123]. CLSs have also been found in the tongues of patients with early-stage squamous cell carcinoma [124], which suggests their multifactorial involvement in cancer development. The formation of CLSs was found to create hypoxic areas, which partially induces ATM transition towards the proinflammatory M1 phenotype via HIF-1α-dependent mechanisms [125]. Remarkably, hypoxia is one of the common processes driven by both ATMs and TAMs [22].

ATMs that populate obese adipose tissue are phenotypically heterogeneous [126]. While most of the macrophages in the adipose tissue of lean mice resemble the alternatively activated M2-like subtype, the majority of ATMs in the adipose tissue of diet-induced obese mice display the M1-like phenotype [127]. Thus, initially, the inflammation of the adipose tissue and the accompanying hyperinsulinemia may allow for the development of insulin-resistant macrophages, which have a reduced capacity to respond to inflammatory stimuli and possess a distinct M2-like phenotype [128]. However, diet-induced obesity in mice was actually shown to cause a shift in the activation state of ATMs in lean animals from an M2-polarized anti-inflammatory state to an M1-polarized proinflammatory state [129,130].

Abundant TAM populations are also found in the stroma of solid tumors and play critical roles in all stages of tumor progression. Multiple distinct phenotypical and functional features have been demonstrated in both ATMs and TAMs, which cohabitate in the adipose TME. TAMs become polarized upon receiving signals from the particular TME in which they reside, and, overall, TAM populations consist of tumor-promoting M2 subtype and a small fraction of antitumor M1 cells (Table 2 and [131]). It has been reported that cancer cells, by scavenging membrane cholesterol from TAMs, induce the reprogramming of TAMs toward the immunosuppressive and tumor-promoting M2 phenotype (Fig. 2 and [132]. However, the interactions of TAMs with cancer cells and other components of the TME are still poorly defined, and multiple populations of TAMs have been detected in multiple tumor settings. Interestingly, although obesity is classically considered a pro-carcinogenic state, conflicting evidence suggests that being overweight and/or obese induces a protective status against certain stages and types of cancer [133] and increases the efficacy of cancer immunotherapy [134]. Such a paradoxical effect has been associated with the leptin-induced repolarization of TAMs from the protumoral M2-like immunosuppressive phenotype to the antitumoral M1-like TAM subtype. Thus, an increase in the leptin level was sufficient to enhance M1-like macrophage polarization in both obese and leptin-treated lean mice, thus reducing tumor growth [135]. This example illustrates the complex and dynamic interactions between the internal metabolic environment of an expanded adipose tissue and the growth and development of a malignant tumor in the adipose TME.

Whether the development of obesity can induce a phenotypic and functional transformation of ATMs into TAMs is not known. Interestingly, it was found that ATMs isolated from obese human subjects, but not human monocyte-derived macrophages isolated from the same patients, resemble TAMs isolated from solid tumors regarding their global gene expression profiles, with the most significant pathways shared between ATMs and TAMs being cancer-related pathways [136]. In line with this finding, it was further reported that obese breast adipose tissue contained increased M2-biased ATMs and that, in comparison with breast tissue macrophages from lean women, they more closely resembled TAMs [137].

4.2. Tumorigenic cancer-associated fibroblast

A major component of the TME is the population of CAFs, which have also been described as promoters of tumor invasion and metastasis [138,139]. There is a consensus statement defining what a CAF is: Cells from tissue biopsy samples with an elongated morphology, lacking the mutations found within cancer cells, and are negative for epithelial, endothelial, and leukocyte markers [139]. However, since there is no specific and unique marker expressed only in CAFs, their identification is not easy. Adipose tissue-derived mesenchymal stromal/stem cells (ASCs) have been shown to de-differentiate into different major subpopulations of CAFs in mice, demonstrating that ASCs are also susceptible to gaining malignant phenotypes in vivo [140]. Notably, obesity seems to fuel this de-differentiation process, since ASCs from obese patients co-cultured with cancer cell lines were shown to express higher levels of CAF markers and promote breast cancer cell proliferation and invasion [141]. ASCs can modulate the metabolism of breast cancer cells by stimulating the upregulation of CD36, increasing the number of lipid droplets [142]. CAFs also originate from endothelial cells through the endothelial-to-mesenchymal transition, which is negatively regulated by FAO [143].

CAFs transfer lipids and proteins to cancer cells through cargo vesicles supporting tumor growth [144]. CAFs also serve as a hub of lipids, acting as fatty acid suppliers to support the metabolic needs of breast and colorectal cancer cells (Table 2 and [145,146]). The CAF population derives in part from tissue-resident pancreatic stellate cells in the TME of pancreatic ductal adenocarcinoma [147]. The differentiation to CAF induces a significant shift in lipid metabolism, secreting abundant lysophosphatidylcholines that support phospholipid synthesis for pancreatic ductal adenocarcinoma cell growth and the facilitation of the production of LPA (Fig. 2 and [148].

4.3. Endothelial cells and angiogenesis

Glucose deprivation or acidosis in the TME promotes endothelial cell proliferation via activating FAO through CPT1 [149,150]. Leptin also has the ability to promote FAO in endothelial cells [151]. Furthermore, endothelial cells respond rapidly to changing environmental situations in the TME because their expression patterns in metabolic-related genes seem to not be homogeneous in different tissues [152]. The proliferation of endothelial cells can be caused by a rise in glycolysis under pathological angiogenic conditions when 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, an essential target of growth factor signaling, is upregulated [153]. However, proliferative endothelial cells have shown an increase in fatty acid uptake [154], and VEGFB plays a role in this process [155]. Lastly, endothelial migration is also regulated by *de novo* fatty acid synthesis via acetyl-CoA carboxylase [156], and, moreover, fatty acid synthase (FAS) is required for angiogenesis [157].

Strong evidence indicates that cholesterol levels regulate angiogenic processes (Fig. 2). Ezetimibe, a cholesterol absorption inhibitor, showed anti-angiogenic effects in mice fed an obesogenic diet [158,159]. Moreover, cholesterol efflux from endothelial cells to HDL reduces lipid rafts, interferes with VEGF receptor 2 (VEGFR2) signaling, and inhibits angiogenesis [160]. In line with these findings, the activation of endothelial LXRs upregulates cholesterol efflux mechanisms and reduces tumor angiogenesis by impairing the compartmentation of VEGFR2 [161]. VEGFB also causes impairment in LDL receptor recycling and thereby reduces cholesterol uptake by endothelial cells [162]. However, its role in the adipose TME is unknown.

CD36 is also presented in endothelial cells and, together with CAA and CAF, controls the bioavailability of long-chain fatty acids in the adipose TME (Table 2 and [163]). Indeed, these systemically mobilized fatty acids are used for breast cancer cell growth in mice [163].

Hypoxia also induces pro-angiogenic signals to support tumor growth, vascular leakiness, and extracellular matrix remodeling. In comparison to the quiescent state of endothelial cells in healthy tissues, the angiogenic features of tumor vessels require a proliferative and migratory state of endothelial cells. The most important players in these processes are VEGFA and angiopoietin-like 4 (ANGPTL4), both secreted as a result of the expansion of the adipose tissue in the context of obesity

[164]. VEGFA acts chiefly on endothelial cells by interacting with VEGFR2, the main mediator of the cellular reaction to the growth factor [165]. The expression of ANGPTL4 disrupts vascular endothelial junctions, increases vessel permeability, and reshapes the transendothelial barriers, ultimately facilitating cancer-cell motility and metastasis [166]. Indeed, the expansion of adipose tissue is coordinated with its vascularization, and adipocytes secrete multiple other proangiogenic factors. For example, leptin and IL-6 produced by obese adipocytes induced the activation, proliferation, and migration of endothelial cells through the upregulation of VEGF and VEGFR-2 [167,168]. Leptin also activates the migration and invasion of gastric cancer cells via AKT and extracellular signal-regulated kinases signaling pathways and upregulating VEGF [169]. The accumulation of LPA in the TME can stimulate the production of IL-8 and prostaglandin E2, which in turn enhances the production of VEGF [170]. Finally, IGF-1/IGF-1R signaling increases alarmin S100A7 production, so activating the Receptor for Advanced Glycation End Products signaling in vascular endothelial cells, ultimately causing an increase in angiogenesis [171].

4.4. $CD8^+$ cytotoxic T cells

Obesity causes opposing lipid metabolic changes in $CD8^+$ T cells versus colorectal, breast adenocarcinoma, and melanoma cancer cells, revealing a new mechanism by which cancer cells change the TME conditions in obesity [172]. This study also reported that cancer and local immune cells compete for fatty acids, and the enhanced fatty acid uptake and FAO in cancer cells blocked fatty acid metabolism in T cells, leading to impaired antitumor immunity (Table 2 and [172]. Importantly, prolyl hydroxylase 3 overexpression impaired cancer cell FAO and improved antitumor immune function in tumor-bearing obese mice [172]. However, obesity-mediated tumor development in the PyMT transgenic mice impaired $CD8^+$ T cell function by reducing glycolysis while promoting FAO via leptin-induced STAT3 activation [173]. These divergent effects of FAO on $CD8^+$ T cell antitumor functions could be related to the lipid-rich environment of the mammary glands [173]. Furthermore, the higher amount of ox-LDL in the obese setting could further impair the intratumoral $CD8^+$ T cell function [174].

5. Potential therapeutic strategies

5.1. Nutritional interventions

Nutritional interventions may provide systemic responses affecting the immune system's antitumoral response as well as a reduction in low-grade chronic inflammation, dyslipidemia, insulin resistance, and/or obesity. In particular, weight loss has been linked to a lower risk of cancer, specifically breast and endometrial cancers in postmenopausal women [175]. This is particularly true for interventions that result in significant and long-term weight loss, such as bariatric surgery [176]. The relation between body weight and breast cancer risk appears to be highly dependent on menopausal status since obesity appears to be protective in premenopausal women [177]. Similarly, the efficacy of fasting cycles or fasting-mimicking diets in slowing tumor development has already been established in experimental models [178,179], and other dietary approaches for cancer therapy are expected to follow. Saturated fat intake has previously been shown to increase the expression of genes associated with inflammation, insulin resistance, hepatic steatosis, and/or cancer risk, whereas certain PUFAs have anticancer properties [180–183]. The two primary PUFA categories, the omega-3 and omega-6 fatty acids, need to be consumed as part of a healthy diet. Epidemiological studies have investigated the function of omega-3 and omega-6 PUFAs in cancer risk, and it was found that consuming a Western diet poor in PUFAs is related to an increased risk of various cancer types [184]. Particularly, an increased intake of omega-3 as well as a greater dietary intake ratio of omega-3: omega-6 PUFAs were associated with a lower risk of breast cancer in obese women but not in overweight or normal-weight women [185], revealing a relationship between obesity, omega-3-PUFA intake, and the risk of breast cancer. Several mechanisms have been proposed to explain the anticarcinogenic effects of omega-3 PUFAs, including changes in the cell plasma membrane composition, the inhibition of the arachidonic acid-derived synthesis of inflammatory eicosanoids, and the altered expression of genes involved in cell proliferation and apoptosis [186]. In line with these findings, the consumption of a Mediterranean diet reduces the expression of genes associated with oxidative stress, inflammation, and/or insulin signaling [187]. Also, a ketogenic diet (a diet low in carbs and high in fat but with the same caloric intake) has been demonstrated to enhance the antitumor efficacy of phosphatidylinositol-3-kinase inhibitors in a preclinical pancreatic ductal adenocarcinomas model [188]. A ketogenic diet has also been proven to reduce the growth of patient-derived xenografts in preclinical models of glioblastoma [189]. Combining a calorie-restricted and ketogenic diet similarly reduced glioblastoma growth, with a significant increase in antitumor activity when paired with the glutamine antagonist 6-diazo-5-oxo-L-norleucine [190]. Mechanistically, energy-restricted diets supplemented with eicosapentaenoic acid and lipoic acid increase the expression of genes involved in FAO while decreasing the expression of genes associated with *de novo* lipogenesis and inflammation [191]. However, the potential of these diets to prevent carcinogenic processes in the setting of obesity remains poorly understood.

A recent review collected data on bioactive compounds from natural sources, including polyphenols (flavonoids, stilbenes, curcuminoids, and phenolic acids) and terpenoids, that could potentially have antitumorigenic activities in the setting of obesity [192]. Precisely, polyphenols assist in the prevention of obesity by modulating genes involved in adipogenesis, lipolysis, and FAO [193]. Natural-source dietary ingredients and nutrients such as epigallocatechin-3-gallate, curcumin, sulforaphane, and genistein have been shown to have anticancer properties, mainly by regulating the expression of lipogenic and FAO genes [192]. It should be noted that oroxylin A, one of the main bioactive flavonoids of the medicinal plant *Scutellaria baicalensis* Georgi, inactivated HIF1α and enhanced FAO, thereby downregulating intracellular fatty acid levels, which leads to the suppression of cell growth and the development of colon cancer [194]. Oroxylin also delayed the progress of primary colon cancer in mice fed an obesogenic diet [194]. Finally, it has also been reported that colorectal cancer is linked to intestinal dysbiosis, and evidence suggests that microbial-derived short-chain fatty acids control inflammation and regulatory T-cell populations [195]. Furthermore, microbial dysbiosis also plays a critical role in the etiology of the colon, gastric, esophageal, pancreatic, laryngeal, breast, and gallbladder carcinomas in close association with host inflammation [196]. Since obese subjects show an altered gut microbiota and a disrupted intestinal epithelium barrier, the development of microbiota-targeting therapies is now considered a potential clinical strategy to prevent obesity-related cancers.

5.2. Drugs targeted to regulate fatty acid metabolism

The inhibition of lipid metabolic enzymes may cause tumor regression, decrease metastatic spread, and/or prevent drug resistance [197], and this could be particularly relevant in the setting of obesity. Regarding lipogenic enzymes, the inhibition of two enzymes, FAS and acetyl-CoA carboxylase, was investigated in early breast cancer models to demonstrate their relevance in the prevention of tumor growth [198]. As such, a first-in-class FAS inhibitor is now in phase II clinical trials due to its anticancer potential [199]. A favorable safety profile and clinical activity were presented in patients with $KRAS^{mut}$ non-small cell lung, breast, and ovarian cancer [199]. As mentioned above, another line of therapy should be focused on FAO reprogramming. Indeed, myeloid-derived suppressor cells, which promote tumor growth by inhibiting T-cell immunity, also prefer FAO over glycolysis, and, thus, therapy with FAO inhibitors might enhance antitumor immunity [200].

In line with these findings, it has been demonstrated that the pharmacological suppression of FAO significantly reduces energy metabolism and, thus, triple-negative breast cancer development in an MYC-dependent manner in experimental models [201].

Concerning lipid uptake, it has been described that the inactivation of CD36 delayed cancer progression in a phosphatase and tensin homolog-deficient murine prostate cancer model, and therapy with a CD36-targeting antibody reduced tumor growth in patient-derived xenografts [202]. Furthermore, metastasis-initiating subpopulations of oral squamous carcinoma cells exhibit elevated CD36 expression and an enhanced propensity to absorb and metabolize fatty acids [203]. Mice fed an obesogenic diet and injected with this group of cells had a greater prevalence of lymph-node metastases [203]. Exposing cancer cells to palmitate before implantation could result in a similar phenotype. Importantly, mice treated with the monoclonal antibody JC63.1, which inhibits CD36 transport activity, had less metastatic formation [203]. It has also been demonstrated that oleate has a proliferative effect on breast cancer cells that is dependent on CD36 since the suppression of CD36 expression has been shown to greatly reduce exogenous fatty acid uptake [204]. Steroyl-CoA desaturase inhibition also yielded pronounced growth inhibition in breast cancer cells [204]. This metabolic reliance could be used therapeutically and be more effective in obese patients.

5.3. Statins

Hypercholesterolemia, an obesity-related co-morbidity, affects roughly 20% of the total adult population in developed countries [205]. Considering the vital and prooncogenic functions of cholesterol in cancer, impeding either cholesterol synthesis or lipoprotein-mediated cholesterol uptake can be a feasible anti-carcinogenesis strategy. Moreover, the significance of cholesterol as a precursor for endogenous sex steroid production suggests that it may be important in both breast and prostate cancer, two hormone-dependent tumor forms. According to several studies, inhibiting the synthesis of cholesterol reduces the growth and transformation of cancer cells [51]. Statin use has been linked to lower total cancer risk [206] and cancer-specific mortality [207] through a variety of potential mechanisms, including the inhibition of the mevalonate pathway that downregulates cholesterol biosynthesis and intermediates that interfere with the post-translational modification and activation of small nucleotide guanosine triphosphate hydrolases and their downstream signaling [208]. Because statins have a limited bioavailability in blood [209], their cholesterol-lowering properties may be the most relevant regarding breast and prostate malignancies. Although several large clinical trials have indicated that statins may reduce the incidence of breast, prostate, pancreatic, and ovarian cancer, these findings could not be reproduced in all studies [51]. The role of hypolipidemic drugs, notably statins, in the prevention and/or therapy of various forms of human cancer is still debatable, and additional properly planned clinical research is required before a more definitive judgment about their ability to lower the risk or recurrence of sex steroid-dependent cancer forms can be made.

5.4. Oral antidiabetic drugs

Oral antidiabetic therapy includes a range of diverse drugs such as biguanides (with metformin as the main exponent) and sodium-glucose transport protein 2 inhibitors (SGLT2i). Epidemiological studies observed a decreased cancer risk in patients treated with metformin, specifically in terms of breast, colorectal, esophageal, liver and pancreatic cancer [210,211]. Metformin was also able to inhibit tumor growth in obese mice models of endometrial cancer [212] and in estrogen-receptor positive breast cancer [213]. The proposed mechanism by which metformin causes tumor suppression is AMP-activated protein kinase (AMPK) activation, which could regulate phospholipid metabolism and inhibit lipogenesis [214,215]. However, not all studies have found a significant reduction in cancer among metformin users [216]. Furthermore, randomized clinical trials only indicate a small benefit [217] or no improvements [218] when metformin is used as adjuvant therapy. The use of SGLT2i was first associated with an increased risk of bladder and breast cancer. Posterior animal and better-powered human studies have not detected this increased risk of cancer [219]. Indeed, SGLT2 inhibition may be an effective way of attenuating liver cancer [220] and increase the sensitivity to chemotherapy in breast cancer cells [221]. SGLT2 inhibitors were able to reduce tumor growth in a mouse model of obesity-associated breast and colon cancer [222]. The mechanisms involved specifically in these findings are complex and still not fully understood; SGLT2i induce AMPK activation and SREBP1 suppression. This results in the suppression of the production of MUFAs and PUFAs and enhanced lipid peroxidation [223].

A detailed list of all potential therapies that could potentially prevent tumorigenic processes associated with lipid metabolic alterations in the obese host macroenvironment and the adipose TME are shown in Table 3**.** The effectiveness of these therapies will be significantly enhanced if body weight, body composition, and other circulating macroenvironmental factors are systematically considered while developing and assessing cancer data. Overall, gaining a greater understanding of the complex interplay between tumor genetics, phenotype, and targeted therapeutic efficacy will allow for the creation of more efficient and customized therapies in obesity-induced lipid alterations in cancer.

6. Concluding remarks

Research on lipid metabolic dysregulation affecting cancer development in the obese setting has attracted great interest in the past decade. Multiple experimental and epidemiological pieces of evidence indicate that obesity worsens the risk and cancer-related mortality of multiple types of cancers. Visceral WAT expansion changes the host macroenvironment and promotes cancer cell growth and invasion by inducing proinflammatory processes, hyperinsulinemia, and dyslipidemia, and increasing the availability of various growth factors (Table 1 and Fig. 1**)**. Indeed, a high BMI is considered to be a modifiable risk factor for cancer. Lipids participate in heterotypic cellular interactions within the adipose TME, shaping the functions of both cancer and non-cancer cells. Importantly, by providing an additional source of fuel, the FFAs released by CAAs facilitate cancer cells' attainment of their high-energy requirements **(**Table 2 and Fig. 2**)**. Therefore, the molecules engaged in crucial processes that lie at the nexus of obesity and cancer represent potential therapeutic targets for upcoming clinical applications. Nutritional interventions, drugs targeting lipid metabolism, and oral antidiabetic drugs appear to be potential therapeutic approaches to prevent the complex cancer-associated metabolic dysregulations in the obese setting.

Funding Source

There was no sponsor involvement in the study design; collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication.

CRediT authorship contribution statement

Miriam Lee-Rueckert: Conceptualization, Writing – original draft, Writing – review & editing. **Marina Canyelles:** Writing – original draft, Writing – review & editing, Funding acquisition. **Mireia Tondo:** Writing – original draft, Writing – review & editing, Funding acquisition. **Noemi Rotllan:** Writing – original draft, Writing – review & editing, Funding acquisition. **Petri T. Kovanen:** Writing – review & editing. **Vicenta Llorente-Cortes:** Writing – original draft, Writing – review & editing, Funding acquisition. **Joan Carles Escolà-Gil:** Conceptualization,

Table 3
Potential therapeutic strategies in obesity-related cancers.

Intervention	Treatment	Mechanisms	Type of Cancer	References
Nutritional interventions	Weight loss	↓ low-grade chronic inflammation ↓ dyslipidemia	Breast and endometrial cancers in postmenopausal women	[175,176, 178]
	Bariatric Surgery	↓ insulin resistance ↓ obesity		
	Fasting	↑ immune system's antitumoral response		
	Omega-3 fatty acid consumption	Changes in cell plasma membrane composition Inhibition of arachidonic-derived synthesis of inflammatory eicosanoids Altered expression of genes involved in cell proliferation and apoptosis	Breast cancer in obese women	[182–186]
	Ketogenic diet	Enhanced efficacy of PI3K inhibitors ↓ the growth of patient-derived xenografts	Preclinical model of pancreatic ductal adenocarcinoma Preclinical model of glioblastoma	[188,189]
	Ketogenic diet + calorie restricted diet + 6-diazo-5-oxo-L-norleucina		Glioblastoma	[190]
	Energy-restricted diet + EPA + lipoic acid	↑ expression of genes involved in FAO ↓ expression of genes associated with *de novo* lipogenesis and inflammation	Not specified	[191]
	Polyphenols and terpenoids	Modulation of genes involved in adipogenesis, lipolysis and FAO	Not specified	[192,193]
	Microbiota targeting therapies	Control inflammation and regulatory T-cell populations	Colon, gastric, esophageal, pancreatic, laryngeal, breast, and gallbladder carcinomas	[195,196]
Therapeutic drugs targeting fatty acid metabolism	Inhibition of FAS and acetyl-CoA carboxylase	Tumor growth prevention	Breast, lung and ovarian cancer	[198,199]
	Inhibition of FAO			[200,201]
		Enhanced T-cell immunity	Breast cancer	
	Inhibition of CD36	↓ exogenous fatty acid uptake	Murine prostate cancer model and breast cancer cells	[202,204]
Lipid metabolism	Statins	Inhibition of cholesterol biosynthesis ↓ serum cholesterol levels ↓ inflammation and angiogenesis	Breast, prostate, pancreatic and ovarian cancer	[51, 206–208]
Antidiabetic drugs	Metformin	Activation of AMPK inhibits fatty acid synthesis and enhances FAO	Not specified	[214,215]
	SGLT2i	↓MUFA and PUFA production as well as enhanced lipid peroxidation due to SREBP1 suppression via AMPK activation	Not specified	[223]

Potential dietary and pharmacological interventions targeting obesity-induced alterations for cancer treatment and prevention. AMPK, AMP-activated protein kinase; CD36, cluster of differentiation 36; EPA, eicosapentaenoic acid; FAO, fatty acid β-oxidation; FAS, fatty acid synthase; MUFA, monounsaturated fatty acids; PI3K, phosphoinositide 3-kinase; PUFA, polyunsaturated fatty acids; SGLT2i, sodium-glucose transport protein 2 inhibitors; SREBP1, sterol regulatory element binding protein 1.

Writing – original draft, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Data Availability

No data was used for the research described in the article.

Acknowledgments

This work was partly funded by the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, and FEDER "Una manera de hacer Europa," grant FIS PI19-00136 and PI21-00140 (to J.C.E.-G. and M.T, respectively) and by grants from the Ministerio de Ciencia, Innovación y Universidades (PID2019-104367RB-100) and Agencia Estatal de Investigación (AEI/10.13039/501100011033) within the Subprograma Ramón y Cajal (RYC-201722879 to NR). This work was also funded by BBVA Foundation Ayudas a Equipos de Investigación 2019 to the project "Translational Molecular Imaging for detection of Cholesterol Entrapment in the Vasculature with 68Ga-labeled LRP1-derived peptides" (to V.Ll.-C). M.C. was supported by a Rio Hortega contract (CM20/00033) and Juan Rodés contract (JR22/00003). CIBERDEM and CIBERCV are Instituto de Salud Carlos III projects. We thank Carla Borràs for her professional support in the design of the figures.

References

[1] WHO (2022). "WHO European Regional Obesity Report", (ed.) WHO. (⟨https://apps.who.int/iris/handle/10665/353747⟩: WHO).
[2] J. Pearson-Stuttard, B. Zhou, V. Kontis, J. Bentham, M.J. Gunter, M. Ezzati, Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment, Lancet Diabetes Endocrinol. 6 (2018) e6–e15, https://doi.org/10.1016/S2213-8587(18)30150-5.
[3] S. Ling, F. Zaccardi, E. Issa, M.J. Davies, K. Khunti, K. Brown, Inequalities in cancer mortality trends in people with type 2 diabetes: 20 year population-based study in England, Diabetologia 66 (2023) 657–673, https://doi.org/10.1007/s00125-022-05854-8.
[4] X. Zhi, X.H. Kuang, K. Liu, J. Li, The global burden and temporal trend of cancer attributable to high body mass index: estimates from the Global Burden of Disease Study 2019, Front Nutr. 9 (2022), 918330, https://doi.org/10.3389/fnut.2022.918330.
[5] R. Baghban, L. Roshangar, R. Jahanban-Esfahlan, K. Seidi, A. Ebrahimi-Kalan, M. Jaymand, et al., Tumor microenvironment complexity and therapeutic implications at a glance, Cell Commun. Signal 18 (2020) 59, https://doi.org/10.1186/s12964-020-0530-4.
[6] W. Al-Zoughbi, G. Hoefler, Tumor Macroenvironment: an Update, Pathobiology 87 (2020) 58–60, https://doi.org/10.1159/000502097.
[7] J. Park, T.S. Morley, M. Kim, D.J. Clegg, P.E. Scherer, Obesity and cancer–mechanisms underlying tumour progression and recurrence, Nat. Rev. Endocrinol. 10 (2014) 455–465, https://doi.org/10.1038/nrendo.2014.94.
[8] K. Esposito, P. Chiodini, A. Colao, A. Lenzi, D. Giugliano, Metabolic syndrome and risk of cancer: a systematic review and meta-analysis, Diabetes Care 35 (2012) 2402–2411, https://doi.org/10.2337/dc12-0336.
[9] B. Peck, A. Schulze, Lipid metabolism at the nexus of diet and tumor microenvironment, Trends Cancer 5 (2019) 693–703, https://doi.org/10.1016/j.trecan.2019.09.007.

[10] D.F. Quail, A.J. Dannenberg, The obese adipose tissue microenvironment in cancer development and progression, Nat. Rev. Endocrinol. 15 (2019) 139–154, https://doi.org/10.1038/s41574-018-0126-x.
[11] B.P. Leitner, S. Huang, R.J. Brychta, C.J. Duckworth, A.S. Baskin, S. McGehee, et al., Mapping of human brown adipose tissue in lean and obese young men, Proc. Natl. Acad. Sci. USA 114 (2017) 8649–8654, https://doi.org/10.1073/pnas.1705287114.
[12] M.M. Ibrahim, Subcutaneous and visceral adipose tissue: structural and functional differences, Obes. Rev. 11 (2010) 11–18, https://doi.org/10.1111/j.1467-789X.2009.00623.x.
[13] P. Trayhurn, J.H. Beattie, Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ, Proc. Nutr. Soc. 60 (2001) 329–339, https://doi.org/10.1079/pns200194.
[14] A.B. Crujeiras, B. Cabia, M.C. Carreira, M. Amil, J. Cueva, S. Andrade, et al., Secreted factors derived from obese visceral adipose tissue regulate the expression of breast malignant transformation genes, *Int J. Obes. (Lond.)* (40 (2016) 514–523, https://doi.org/10.1038/ijo.2015.208.
[15] B. Cannon, J. Nedergaard, Brown adipose tissue: function and physiological significance, Physiol. Rev. 84 (2004) 277–359, https://doi.org/10.1152/physrev.00015.2003.
[16] F. Omran, M. Christian, Inflammatory Signaling and Brown Fat Activity, Front Endocrinol. (Lausanne) 11 (2020) 156, https://doi.org/10.3389/fendo.2020.00156.
[17] E.H. Allott, E.M. Masko, S.J. Freedland, Obesity and prostate cancer: weighing the evidence, Eur. Urol. 63 (2013) 800–809, https://doi.org/10.1016/j.eururo.2012.11.013.
[18] D.M. Huffman, M.S. Johnson, A. Watts, A. Elgavish, I.A. Eltoum, T.R. Nagy, Cancer progression in the transgenic adenocarcinoma of mouse prostate mouse is related to energy balance, body mass, and body composition, but not food intake, Cancer Res 67 (2007) 417–424, https://doi.org/10.1158/0008-5472.CAN-06-1244.
[19] S.A. Bos, C.M. Gill, E.L. Martinez-Salazar, M. Torriani, M.A. Bredella, Preliminary investigation of brown adipose tissue assessed by PET/CT and cancer activity, Skelet. Radio. 48 (2019) 413–419, https://doi.org/10.1007/s00256-018-3046-x.
[20] A.S. Becker, C. Zellweger, S. Bacanovic, S. Franckenberg, H.W. Nagel, L. Frick, et al., Brown fat does not cause cachexia in cancer patients: a large retrospective longitudinal FDG-PET/CT cohort study, PLoS One 15 (2020), e0239990, https://doi.org/10.1371/journal.pone.0239990.
[21] A. Alvarez-Artime, B. Garcia-Soler, R.M. Sainz, J.C. Mayo, Emerging roles for browning of white adipose tissue in prostate cancer malignant behaviour, Int J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms22115560.
[22] E. Lengyel, L. Makowski, J. DiGiovanni, M.G. Kolonin, Cancer as a matter of fat: the crosstalk between adipose tissue and tumors, Trends Cancer 4 (2018) 374–384, https://doi.org/10.1016/j.trecan.2018.03.004.
[23] M. Esteve Rafols, Adipose tissue: cell heterogeneity and functional diversity, Endocrinol. Nutr. 61 (2014) 100–112, https://doi.org/10.1016/j.endonu.2013.03.011.
[24] N. Hetemaki, T.S. Mikkola, M.J. Tikkanen, F. Wang, E. Hamalainen, U. Turpeinen, et al., Adipose tissue estrogen production and metabolism in premenopausal women, J. Steroid Biochem Mol. Biol. 209 (2021), 105849, https://doi.org/10.1016/j.jsbmb.2021.105849.
[25] A. Chaplin, R.M. Rodriguez, J.J. Segura-Sampedro, A. Ochogavia-Segui, D. Romaguera, G. Barcelo-Coblijn, Insights behind the relationship between colorectal cancer and obesity: is visceral adipose tissue the missing link, Int J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms232113128.
[26] C.L. Donohoe, J. Lysaght, J. O'Sullivan, J.V. Reynolds, Emerging concepts linking obesity with the hallmarks of cancer, Trends Endocrinol. Metab. 28 (2017) 46–62, https://doi.org/10.1016/j.tem.2016.08.004.
[27] M.P. Czech, M. Tencerova, D.J. Pedersen, M. Aouadi, Insulin signalling mechanisms for triacylglycerol storage, Diabetologia 56 (2013) 949–964, https://doi.org/10.1007/s00125-013-2869-1.
[28] J.C. Heuson, N. Legros, R. Heimann, Influence of insulin administration on growth of the 7,12-dimethylbenz(a)anthracene-induced mammary carcinoma in intact, oophorectomized, and hypophysectomized rats, Cancer Res 32 (1972) 233–238.
[29] D.E. Corpet, C. Jacquinet, G. Peiffer, S. Tache, Insulin injections promote the growth of aberrant crypt foci in the colon of rats, Nutr. Cancer 27 (1997) 316–320, https://doi.org/10.1080/01635589709514543.
[30] A.M.Y. Zhang, E.A. Wellberg, J.L. Kopp, J.D. Johnson, Hyperinsulinemia in obesity, inflammation, and cancer, Diabetes Metab. J. 45 (2021) 285–311, https://doi.org/10.4093/dmj.2020.0250.
[31] A.G. Renehan, J. Frystyk, A. Flyvbjerg, Obesity and cancer risk: the role of the insulin-IGF axis, Trends Endocrinol. Metab. 17 (2006) 328–336, https://doi.org/10.1016/j.tem.2006.08.006.
[32] E.J. Gallagher, D. LeRoith, Minireview: IGF, insulin, and cancer, Endocrinology 152 (2011) 2546–2551, https://doi.org/10.1210/en.2011-0231.
[33] E.J. Gallagher, D. LeRoith, Hyperinsulinaemia in cancer, Nat. Rev. Cancer 20 (2020) 629–644, https://doi.org/10.1038/s41568-020-0295-5.
[34] A. Belfiore, R. Malaguarnera, V. Vella, M.C. Lawrence, L. Sciacca, F. Frasca, et al., Insulin receptor isoforms in physiology and disease: an updated view, Endocr. Rev. 38 (2017) 379–431, https://doi.org/10.1210/er.2017-00073.
[35] D. Foti, R. Iuliano, E. Chiefari, A. Brunetti, A nucleoprotein complex containing Sp1, C/EBP beta, and HMGI-Y controls human insulin receptor gene transcription, Mol. Cell Biol. 23 (2003) 2720–2732, https://doi.org/10.1128/MCB.23.8.2720-2732.2003.
[36] N.J. Webster, J.L. Resnik, D.B. Reichart, B. Strauss, M. Haas, B.L. Seely, Repression of the insulin receptor promoter by the tumor suppressor gene product p53: a possible mechanism for receptor overexpression in breast cancer, Cancer Res 56 (1996) 2781–2788.
[37] H. Endogenous, G. Breast Cancer Collaborative, T.J. Key, P.N. Appleby, G. K. Reeves, A.W. Roddam, et al., Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies, Br. J. Cancer 105 (2011) 709–722, https://doi.org/10.1038/bjc.2011.254.
[38] G. Schneider, M.A. Kirschner, R. Berkowitz, N.H. Ertel, Increased estrogen production in obese men, J. Clin. Endocrinol. Metab. 48 (1979) 633–638, https://doi.org/10.1210/jcem-48-4-633.
[39] L.A. Brinton, M.B. Cook, V. McCormack, K.C. Johnson, H. Olsson, J. T. Casagrande, et al., Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results, J. Natl. Cancer Inst. 106 (2014) djt465, https://doi.org/10.1093/jnci/djt465.
[40] L. Alexandre, E. Long, I.L. Beales, Pathophysiological mechanisms linking obesity and esophageal adenocarcinoma, World J. Gastrointest. Pathophysiol. 5 (2014) 534–549, https://doi.org/10.4291/wjgp.v5.i4.534.
[41] F. Sanchez-Jimenez, A. Perez-Perez, L. de la Cruz-Merino, V. Sanchez-Margalet, Obesity and breast cancer: role of leptin, Front Oncol. 9 (2019) 596, https://doi.org/10.3389/fonc.2019.00596.
[42] L. Catrysse, G. van Loo, Inflammation and the metabolic syndrome: the tissue-specific functions of NF-kappaB, Trends Cell Biol. 27 (2017) 417–429, https://doi.org/10.1016/j.tcb.2017.01.006.
[43] K. Taniguchi, M. Karin, NF-kappaB, inflammation, immunity and cancer: coming of age, Nat. Rev. Immunol. 18 (2018) 309–324, https://doi.org/10.1038/nri.2017.142.
[44] J. Vekic, A. Zeljkovic, A. Stefanovic, Z. Jelic-Ivanovic, V. Spasojevic-Kalimanovska, Obesity and dyslipidemia, Metabolism 92 (2019) 71–81, https://doi.org/10.1016/j.metabol.2018.11.005.
[45] T. Weinbrenner, H. Schroder, V. Escurriol, M. Fito, R. Elosua, J. Vila, et al., Circulating oxidized LDL is associated with increased waist circumference independent of body mass index in men and women, quiz 181-182, Am. J. Clin. Nutr. 83 (2006) 30–35, https://doi.org/10.1093/ajcn/83.1.30.
[46] W.A. Keshk, D.H. Zineldeen, R.E. Wasfy, O.H. El-Khadrawy, Fatty acid synthase/oxidized low-density lipoprotein as metabolic oncogenes linking obesity to colon cancer via NF-kappa B in Egyptians, Med Oncol. 31 (2014) 192, https://doi.org/10.1007/s12032-014-0192-4.
[47] D.J. Silver, G.A. Roversi, N. Bithi, S.Z. Wang, K.M. Troike, C.K. Neumann, et al., Severe consequences of a high-lipid diet include hydrogen sulfide dysfunction and enhanced aggression in glioblastoma, J. Clin. Invest 131 (2021), https://doi.org/10.1172/JCI138276.
[48] M.G. Vander Heiden, L.C. Cantley, C.B. Thompson, Understanding the Warburg effect: the metabolic requirements of cell proliferation, Science 324 (2009) 1029–1033, https://doi.org/10.1126/science.1160809.
[49] M.T. Snaebjornsson, S. Janaki-Raman, A. Schulze, Greasing the wheels of the cancer machine: the role of lipid metabolism in cancer, Cell Metab. 31 (2020) 62–76, https://doi.org/10.1016/j.cmet.2019.11.010.
[50] A.J. Hoy, S.R. Nagarajan, L.M. Butler, Tumour fatty acid metabolism in the context of therapy resistance and obesity, Nat. Rev. Cancer 21 (2021) 753–766, https://doi.org/10.1038/s41568-021-00388-4.
[51] G. Revilla, L. Cedo, M. Tondo, A. Moral, J.I. Perez, R. Corcoy, et al., LDL, HDL and endocrine-related cancer: From pathogenic mechanisms to therapies, Semin Cancer Biol. 73 (2021) 134–157, https://doi.org/10.1016/j.semcancer.2020.11.012.
[52] R.L. Silverstein, M. Febbraio, CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior, Sci. Signal 2 (2009) re3, https://doi.org/10.1126/scisignal.272re3.
[53] J.A. Menendez, R. Lupu, Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis, Nat. Rev. Cancer 7 (2007) 763–777, https://doi.org/10.1038/nrc2222.
[54] R.J. Veldman, K. Klappe, J. Hinrichs, I. Hummel, G. van der Schaaf, H. Sietsma, et al., Altered sphingolipid metabolism in multidrug-resistant ovarian cancer cells is due to uncoupling of glycolipid biosynthesis in the Golgi apparatus, FASEB J. 16 (2002) 1111–1113, https://doi.org/10.1096/fj.01-0863fje.
[55] A. Mannechez, P. Reungpatthanaphong, J.D. de Certaines, G. Leray, L. Le Moyec, Proton NMR visible mobile lipid signals in sensitive and multidrug-resistant K562 cells are modulated by rafts, Cancer Cell Int. 5 (2005) 2, https://doi.org/10.1186/1475-2867-5-2.
[56] A.M. Gouw, K. Margulis, N.S. Liu, S.J. Raman, A. Mancuso, G.G. Toal, et al., The MYC oncogene cooperates with sterol-regulated element-binding protein to regulate lipogenesis essential for neoplastic growth, e555, Cell Metab. 30 (2019) 556–572, https://doi.org/10.1016/j.cmet.2019.07.012.
[57] L.M. Butler, Y. Perone, J. Dehairs, L.E. Lupien, V. de Laat, A. Talebi, et al., Lipids and cancer: emerging roles in pathogenesis, diagnosis and therapeutic intervention, Adv. Drug Deliv. Rev. 159 (2020) 245–293, https://doi.org/10.1016/j.addr.2020.07.013.
[58] Y. Xu, Targeting lysophosphatidic acid in cancer: the issues in moving from bench to bedside, *Cancers (Basel)* (11 (2019), https://doi.org/10.3390/cancers11101523.
[59] S. Ehmsen, M.H. Pedersen, G. Wang, M.G. Terp, A. Arslanagic, B.L. Hood, et al., Increased cholesterol biosynthesis is a key characteristic of breast cancer stem cells influencing patient outcome, e3926, Cell Rep. 27 (2019) 3927–3938, https://doi.org/10.1016/j.celrep.2019.05.104.
[60] F. Guillaumond, G. Bidaut, M. Ouaissi, S. Servais, V. Gouirand, O. Olivares, et al., Cholesterol uptake disruption, in association with chemotherapy, is a promising

combined metabolic therapy for pancreatic adenocarcinoma, Proc. Natl. Acad. Sci. USA 112 (2015) 2473–2478, https://doi.org/10.1073/pnas.1421601112.
[61] C. Garcia-Ruiz, L. Conde de la Rosa, V. Ribas, J.C. Fernandez-Checa, Mitochondrial cholesterol and cancer, Semin Cancer Biol. 73 (2021) 76–85, https://doi.org/10.1016/j.semcancer.2020.07.014.
[62] A. Shamma, Y. Takegami, T. Miki, S. Kitajima, M. Noda, T. Obara, et al., Rb regulates DNA damage response and cellular senescence through E2F-dependent suppression of N-ras isoprenylation, Cancer Cell 15 (2009) 255–269, https://doi.org/10.1016/j.ccr.2009.03.001.
[63] Y. Ma, S.M. Temkin, A.M. Hawkridge, C. Guo, W. Wang, X.Y. Wang, et al., Fatty acid oxidation: An emerging facet of metabolic transformation in cancer, Cancer Lett. 435 (2018) 92–100, https://doi.org/10.1016/j.canlet.2018.08.006.
[64] J.E. Druso, C. Fischbach, Biophysical properties of extracellular matrix: linking obesity and cancer, Trends Cancer 4 (2018) 271–273, https://doi.org/10.1016/j.trecan.2018.02.001.
[65] B.R. Seo, P. Bhardwaj, S. Choi, J. Gonzalez, R.C. Andresen Eguiluz, K. Wang, et al., Obesity-dependent changes in interstitial ECM mechanics promote breast tumorigenesis, Sci. Transl. Med 7 (2015) 301ra130, https://doi.org/10.1126/scitranslmed.3010467.
[66] S.C. Wei, L. Fattet, J.H. Tsai, Y. Guo, V.H. Pai, H.E. Majeski, et al., Matrix stiffness drives epithelial-mesenchymal transition and tumour metastasis through a TWIST1-G3BP2 mechanotransduction pathway, Nat. Cell Biol. 17 (2015) 678–688, https://doi.org/10.1038/ncb3157.
[67] S. Appunni, M. Rubens, V. Ramamoorthy, V. Anand, M. Khandelwal, A. Sharma, Biglycan: an emerging small leucine-rich proteoglycan (SLRP) marker and its clinicopathological significance, Mol. Cell Biochem 476 (2021) 3935–3950, https://doi.org/10.1007/s11010-021-04216-z.
[68] A.R. Pessentheiner, G.M. Ducasa, P. Gordts, Proteoglycans in obesity-associated metabolic dysfunction and meta-inflammation, Front Immunol. 11 (2020) 769, https://doi.org/10.3389/fimmu.2020.00769.
[69] M. Kim, C. Lee, J. Park, Extracellular matrix remodeling facilitates obesity-associated cancer progression, Trends Cell Biol. 32 (2022) 825–834, https://doi.org/10.1016/j.tcb.2022.02.008.
[70] G. Martinez-Santibanez, K.W. Cho, C.N. Lumeng, Imaging white adipose tissue with confocal microscopy, Methods Enzym. 537 (2014) 17–30, https://doi.org/10.1016/B978-0-12-411619-1.00002-1.
[71] C. Corbet, A. Pinto, R. Martherus, J.P. Santiago de Jesus, F. Polet, O. Feron, Acidosis drives the reprogramming of fatty acid metabolism in cancer cells through changes in mitochondrial and histone acetylation, Cell Metab. 24 (2016) 311–323, https://doi.org/10.1016/j.cmet.2016.07.003.
[72] W.S. Yang, K.J. Kim, M.M. Gaschler, M. Patel, M.S. Shchepinov, B.R. Stockwell, Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis, Proc. Natl. Acad. Sci. USA 113 (2016) E4966–E4975, https://doi.org/10.1073/pnas.1603244113.
[73] J. Xiao, K. Shen, K. Liu, Y. Wang, H. Fan, Q. Cheng, et al., Obesity promotes lipid accumulation in lymph node metastasis of gastric cancer: a retrospective case-control study, Lipids Health Dis. 21 (2022) 123, https://doi.org/10.1186/s12944-022-01734-7.
[74] H. Yao, S. He, Multi-faceted role of cancer-associated adipocytes in the tumor microenvironment (Review, Mol. Med Rep. 24 (2021), https://doi.org/10.3892/mmr.2021.12506.
[75] D. Yang, Y. Li, L. Xing, Y. Tan, J. Sun, B. Zeng, et al., Utilization of adipocyte-derived lipids and enhanced intracellular trafficking of fatty acids contribute to breast cancer progression, Cell Commun. Signal 16 (2018) 32, https://doi.org/10.1186/s12964-018-0221-6.
[76] I. Mentoor, A.M. Engelbrecht, P.J. van Jaarsveld, T. Nell, Chemoresistance: intricate interplay between breast tumor cells and adipocytes in the tumor microenvironment, Front Endocrinol. (Lausanne) 9 (2018) 758, https://doi.org/10.3389/fendo.2018.00758.
[77] A. Benitez-Amaro, N. Martinez-Bosch, N. Manero-Ruperez, L. Claudi, M.T. La Chica Lhoest, M. Soler, et al., Peptides against low density lipoprotein (LDL) aggregation inhibit intracellular cholesteryl ester loading and proliferation of pancreatic tumor cells, Cancers (14 (2022), https://doi.org/10.3390/cancers14040890.
[78] P. Costales, P. Fuentes-Prior, J. Castellano, E. Revuelta-Lopez, M.A. Corral-Rodriguez, L. Nasarre, et al., K domain CR9 of low density lipoprotein (LDL) receptor-related protein 1 (LRP1) is critical for aggregated LDL-induced foam cell formation from human vascular smooth muscle cells, J. Biol. Chem. 290 (2015) 14852–14865, https://doi.org/10.1074/jbc.M115.638361.
[79] A. Gheysarzadeh, A. Ansari, M.H. Emami, A.E. Razavi, M.R. Mofid, Over-expression of low-density lipoprotein receptor-related Protein-1 is associated with poor prognosis and invasion in pancreatic ductal adenocarcinoma, Pancreatology 19 (2019) 429–435, https://doi.org/10.1016/j.pan.2019.02.012.
[80] L.E. Lupien, K. Bloch, J. Dehairs, N.A. Traphagen, W.W. Feng, W.L. Davis, et al., Endocytosis of very low-density lipoproteins: an unexpected mechanism for lipid acquisition by breast cancer cells, J. Lipid Res. 61 (2020) 205–218, https://doi.org/10.1194/jlr.RA119000327.
[81] E.E. Morin, X.A. Li, A. Schwendeman, HDL in endocrine carcinomas: biomarker, drug carrier, and potential therapeutic, Front Endocrinol. (Lausanne) 9 (2018) 715, https://doi.org/10.3389/fendo.2018.00715.
[82] A. Ossoli, E. Giorgio, F. Cetti, M. Ruscica, C. Rabacchi, P. Tarugi, et al., HDL-mediated reduction of cholesterol content inhibits the proliferation of prostate cancer cells induced by LDL: Role of ABCA1 and proteasome inhibition, Biofactors 48 (2022) 707–717, https://doi.org/10.1002/biof.1845.
[83] S.C. Delk, A. Chattopadhyay, J.C. Escola-Gil, A.M. Fogelman, S.T. Reddy, Apolipoprotein mimetics in cancer, Semin Cancer Biol. 73 (2021) 158–168, https://doi.org/10.1016/j.semcancer.2020.11.002.
[84] T.J. Zhao, N. Zhu, Y.N. Shi, Y.X. Wang, C.J. Zhang, C.F. Deng, et al., Targeting HDL in tumor microenvironment: New hope for cancer therapy, J. Cell Physiol. 236 (2021) 7853–7873, https://doi.org/10.1002/jcp.30412.
[85] A. Ossoli, A. Wolska, A.T. Remaley, M. Gomaraschi, High-density lipoproteins: a promising tool against cancer, Biochim Biophys. Acta Mol. Cell Biol. Lipids 1867 (2022), 159068, https://doi.org/10.1016/j.bbalip.2021.159068.
[86] A.L. Harris, Hypoxia–a key regulatory factor in tumour growth, Nat. Rev. Cancer 2 (2002) 38–47, https://doi.org/10.1038/nrc704.
[87] S.K. Parks, J. Chiche, J. Pouyssegur, Disrupting proton dynamics and energy metabolism for cancer therapy, Nat. Rev. Cancer 13 (2013) 611–623, https://doi.org/10.1038/nrc3579.
[88] P.P. Provenzano, S.R. Hingorani, Hyaluronan, fluid pressure, and stromal resistance in pancreas cancer, Br. J. Cancer 108 (2013) 1–8, https://doi.org/10.1038/bjc.2012.569.
[89] Y. Ye, X. Sun, Y. Lu, Obesity-related fatty acid and cholesterol metabolism in cancer-associated host cells, Front Cell Dev. Biol. 8 (2020), 600350, https://doi.org/10.3389/fcell.2020.600350.
[90] K. Oorni, K. Rajamaki, S.D. Nguyen, K. Lahdesmaki, R. Plihtari, M. Lee-Rueckert, et al., Acidification of the intimal fluid: the perfect storm for atherogenesis, J. Lipid Res 56 (2015) 203–214, https://doi.org/10.1194/jlr.R050252.
[91] S. Burgdorf, S. Porubsky, A. Marx, Z.V. Popovic, Cancer acidity and hypertonicity contribute to dysfunction of tumor-associated dendritic cells: potential impact on antigen cross-presentation machinery, Cancers 12 (2020), https://doi.org/10.3390/cancers12092403.
[92] M. Soltani, M. Souri, F. Moradi Kashkooli, Effects of hypoxia and nanocarrier size on pH-responsive nano-delivery system to solid tumors, Sci. Rep. 11 (2021) 19350, https://doi.org/10.1038/s41598-021-98638-w.
[93] C.A. Lewis, C. Brault, B. Peck, K. Bensaad, B. Griffiths, R. Mitter, et al., SREBP maintains lipid biosynthesis and viability of cancer cells under lipid- and oxygen-deprived conditions and defines a gene signature associated with poor survival in glioblastoma multiforme, Oncogene 34 (2015) 5128–5140, https://doi.org/10.1038/onc.2014.439.
[94] R.C. Sun, N.C. Denko, Hypoxic regulation of glutamine metabolism through HIF1 and SIAH2 supports lipid synthesis that is necessary for tumor growth, Cell Metab. 19 (2014) 285–292, https://doi.org/10.1016/j.cmet.2013.11.022.
[95] B. Peck, A. Schulze, Lipid desaturation - the next step in targeting lipogenesis in cancer, FEBS J. 283 (2016) 2767–2778, https://doi.org/10.1111/febs.13681.
[96] B.T. Finicle, V. Jayashankar, A.L. Edinger, Nutrient scavenging in cancer, Nat. Rev. Cancer 18 (2018) 619–633, https://doi.org/10.1038/s41568-018-0048-x.
[97] Q. Wu, B. Li, J. Li, S. Sun, J. Yuan, S. Sun, Cancer-associated adipocytes as immunomodulators in cancer, Biomark. Res 9 (2021) 2, https://doi.org/10.1186/s40364-020-00257-6.
[98] K.M. Nieman, H.A. Kenny, C.V. Penicka, A. Ladanyi, R. Buell-Gutbrod, M. R. Zillhardt, et al., Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth, Nat. Med 17 (2011) 1498–1503, https://doi.org/10.1038/nm.2492.
[99] Y.Y. Wang, C. Attane, D. Milhas, B. Dirat, S. Dauvillier, A. Guerard, et al., Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells, JCI Insight 2 (2017), e87489, https://doi.org/10.1172/jci.insight.87489.
[100] S. Balaban, R.F. Shearer, L.S. Lee, M. van Geldermalsen, M. Schreuder, H. C. Shtein, et al., Adipocyte lipolysis links obesity to breast cancer growth: adipocyte-derived fatty acids drive breast cancer cell proliferation and migration, Cancer Metab. 5 (2017) 1, https://doi.org/10.1186/s40170-016-0163-7.
[101] E. Clement, I. Lazar, C. Attane, L. Carrie, S. Dauvillier, M. Ducoux-Petit, et al., Adipocyte extracellular vesicles carry enzymes and fatty acids that stimulate mitochondrial metabolism and remodeling in tumor cells, EMBO J. 39 (2020), e102525, https://doi.org/10.15252/embj.2019102525.
[102] D.K. Nomura, J.Z. Long, S. Niessen, H.S. Hoover, S.W. Ng, B.F. Cravatt, Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis, Cell 140 (2010) 49–61, https://doi.org/10.1016/j.cell.2009.11.027.
[103] E.R. Nelson, S.E. Wardell, J.S. Jasper, S. Park, S. Suchindran, M.K. Howe, et al., 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology, Science 342 (2013) 1094–1098, https://doi.org/10.1126/science.1241908.
[104] D.W. Russell, Oxysterol biosynthetic enzymes, Biochim Biophys. Acta 1529 (2000) 126–135, https://doi.org/10.1016/s1388-1981(00)00142-6.
[105] A.E. Baek, Y.A. Yu, S. He, S.E. Wardell, C.Y. Chang, S. Kwon, et al., The cholesterol metabolite 27 hydroxycholesterol facilitates breast cancer metastasis through its actions on immune cells, Nat. Commun. 8 (2017) 864, https://doi.org/10.1038/s41467-017-00910-z.
[106] Q. Wu, T. Ishikawa, R. Sirianni, H. Tang, J.G. McDonald, I.S. Yuhanna, et al., 27-Hydroxycholesterol promotes cell-autonomous, ER-positive breast cancer growth, Cell Rep. 5 (2013) 637–645, https://doi.org/10.1016/j.celrep.2013.10.006.
[107] D. Zhu, Z. Shen, J. Liu, J. Chen, Y. Liu, C. Hu, et al., The ROS-mediated activation of STAT-3/VEGF signaling is involved in the 27-hydroxycholesterol-induced angiogenesis in human breast cancer cells, Toxicol. Lett. 264 (2016) 79–86, https://doi.org/10.1016/j.toxlet.2016.11.006.
[108] C.G. Torres, M.E. Ramirez, P. Cruz, M.J. Epunan, L.E. Valladares, W.D. Sierralta, 27-hydroxycholesterol induces the transition of MCF7 cells into a mesenchymal phenotype, Oncol. Rep. 26 (2011) 389–397, https://doi.org/10.3892/or.2011.1284.

[109] Z. Shen, D. Zhu, J. Liu, J. Chen, Y. Liu, C. Hu, et al., 27-Hydroxycholesterol induces invasion and migration of breast cancer cells by increasing MMP9 and generating EMT through activation of STAT-3, Environ. Toxicol. Pharm. 51 (2017) 1–8, https://doi.org/10.1016/j.etap.2017.02.001.
[110] S. Raza, M. Meyer, J. Schommer, K.D. Hammer, B. Guo, O. Ghribi, 27-Hydroxycholesterol stimulates cell proliferation and resistance to docetaxel-induced apoptosis in prostate epithelial cells, Med Oncol. 33 (2016) 12, https://doi.org/10.1007/s12032-015-0725-5.
[111] D.A. Gibson, F. Collins, F.L. Cousins, A. Esnal Zufiaurre, P.T.K. Saunders, The impact of 27-hydroxycholesterol on endometrial cancer proliferation, Endocr. Relat. Cancer 25 (2018) 381–391, https://doi.org/10.1530/ERC-17-0449.
[112] G. Revilla, M.P. Pons, L. Baila-Rueda, A. Garcia-Leon, D. Santos, A. Cenarro, et al., Cholesterol and 27-hydroxycholesterol promote thyroid carcinoma aggressiveness, Sci. Rep. 9 (2019) 10260, https://doi.org/10.1038/s41598-019-46727-2.
[113] S. He, L. Ma, A.E. Baek, A. Vardanyan, V. Vembar, J.J. Chen, et al., Host CYP27A1 expression is essential for ovarian cancer progression, Endocr. Relat. Cancer 26 (2019) 659–675, https://doi.org/10.1530/ERC-18-0572.
[114] G. Eibinger, G. Fauler, E. Bernhart, S. Frank, A. Hammer, A. Wintersperger, et al., On the role of 25-hydroxycholesterol synthesis by glioblastoma cell lines. Implications for chemotactic monocyte recruitment, Exp. Cell Res 319 (2013) 1828–1838, https://doi.org/10.1016/j.yexcr.2013.03.025.
[115] R. Lappano, A.G. Recchia, E.M. De Francesco, T. Angelone, M.C. Cerra, D. Picard, et al., The cholesterol metabolite 25-hydroxycholesterol activates estrogen receptor alpha-mediated signaling in cancer cells and in cardiomyocytes, PLoS One 6 (2011), e16631, https://doi.org/10.1371/journal.pone.0016631.
[116] L. Cassetta, E. Cassol, G. Poli, Macrophage polarization in health and disease, ScientificWorldJournal 11 (2011) 2391–2402, https://doi.org/10.1100/2011/213962.
[117] O. Kolliniati, E. Ieronymaki, E. Vergadi, C. Tsatsanis, Metabolic regulation of macrophage activation, J. Innate Immun. 14 (2022) 51–68, https://doi.org/10.1159/000516780.
[118] K. Man, A. Kallies, A. Vasanthakumar, Resident and migratory adipose immune cells control systemic metabolism and thermogenesis, Cell Mol. Immunol. 19 (2022) 421–431, https://doi.org/10.1038/s41423-021-00804-7.
[119] H. Kanda, S. Tateya, Y. Tamori, K. Kotani, K. Hiasa, R. Kitazawa, et al., MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity, J. Clin. Invest 116 (2006) 1494–1505, https://doi.org/10.1172/JCI26498.
[120] S.P. Weisberg, D. McCann, M. Desai, M. Rosenbaum, R.L. Leibel, A. W. Ferrante Jr., Obesity is associated with macrophage accumulation in adipose tissue, J. Clin. Invest 112 (2003) 1796–1808, https://doi.org/10.1172/JCI19246.
[121] R. Cancello, J. Tordjman, C. Poitou, G. Guilhem, J.L. Bouillot, D. Hugol, et al., Increased infiltration of macrophages in omental adipose tissue is associated with marked hepatic lesions in morbid human obesity, Diabetes 55 (2006) 1554–1561, https://doi.org/10.2337/db06-0133.
[122] N.M. Iyengar, K.A. Brown, X.K. Zhou, A. Gucalp, K. Subbaramaiah, D.D. Giri, et al., Metabolic obesity, adipose inflammation and elevated breast aromatase in women with normal body mass index, Cancer Prev. Res. 10 (2017) 235–243, https://doi.org/10.1158/1940-6207.CAPR-16-0314.
[123] J.M. Carter, T.L. Hoskin, M.A. Pena, R. Brahmbhatt, S.J. Winham, M.H. Frost, et al., Macrophagic "crown-like structures" are associated with an increased risk of breast cancer in benign breast disease, Cancer Prev. Res (Philos.) 11 (2018) 113–119, https://doi.org/10.1158/1940-6207.CAPR-17-0245.
[124] N.M. Iyengar, R.A. Ghossein, L.G. Morris, X.K. Zhou, A. Kochhar, P.G. Morris, et al., White adipose tissue inflammation and cancer-specific survival in patients with squamous cell carcinoma of the oral tongue, Cancer 122 (2016) 3794–3802, https://doi.org/10.1002/cncr.30251.
[125] S. Fujisaka, I. Usui, M. Ikutani, A. Aminuddin, A. Takikawa, K. Tsuneyama, et al., Adipose tissue hypoxia induces inflammatory M1 polarity of macrophages in an HIF-1alpha-dependent and HIF-1alpha-independent manner in obese mice, Diabetologia 56 (2013) 1403–1412, https://doi.org/10.1007/s00125-013-2885-1.
[126] P. Li, M. Lu, M.T.A. Nguyen, E.J. Bae, J. Chapman, D. Feng, et al., Functional heterogeneity of CD11c-positive adipose tissue macrophages in diet-induced obese mice, J. Biol. Chem. 285 (2010) 15333–15345, https://doi.org/10.1074/jbc.M110.100263.
[127] C.N. Lumeng, J.B. DelProposto, D.J. Westcott, A.R. Saltiel, Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes, Diabetes 57 (2008) 3239–3246, https://doi.org/10.2337/db08-0872.
[128] E. Ieronymaki, E.M. Theodorakis, K. Lyroni, E. Vergadi, E. Lagoudaki, A. Al-Qahtani, et al., Insulin resistance in macrophages alters their metabolism and promotes an M2-like phenotype, J. Immunol. 202 (2019) 1786–1797, https://doi.org/10.4049/jimmunol.1800065.
[129] C.N. Lumeng, J.L. Bodzin, A.R. Saltiel, Obesity induces a phenotypic switch in adipose tissue macrophage polarization, J. Clin. Invest 117 (2007) 175–184, https://doi.org/10.1172/JCI29881.
[130] A. Kosteli, E. Sugaru, G. Haemmerle, J.F. Martin, J. Lei, R. Zechner, et al., Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue, J. Clin. Invest 120 (2010) 3466–3479, https://doi.org/10.1172/JCI42845.
[131] M. Lee-Rueckert, J. Lappalainen, P.T. Kovanen, J.C. Escola-Gil, Lipid-laden macrophages and inflammation in atherosclerosis and cancer: an integrative view, Front Cardiovasc Med 9 (2022), 777822, https://doi.org/10.3389/fcvm.2022.777822.
[132] P. Goossens, J. Rodriguez-Vita, A. Etzerodt, M. Masse, O. Rastoin, V. Gouirand, et al., Membrane cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression, e1374, Cell Metab. 29 (2019) 1376–1389, https://doi.org/10.1016/j.cmet.2019.02.016.
[133] H. Lennon, M. Sperrin, E. Badrick, A.G. Renehan, The obesity paradox in cancer: a review, Curr. Oncol. Rep. 18 (2016) 56, https://doi.org/10.1007/s11912-016-0539-4.
[134] Z. Wang, E.G. Aguilar, J.I. Luna, C. Dunai, L.T. Khuat, C.T. Le, et al., Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade, Nat. Med 25 (2019) 141–151, https://doi.org/10.1038/s41591-018-0221-5.
[135] S.O. Dudzinski, J.E. Bader, K.E. Beckermann, K.L. Young, R. Hongo, M.Z. Madden, et al., Leptin augments antitumor immunity in obesity by repolarizing tumor-associated macrophages, J. Immunol. 207 (2021) 3122–3130, https://doi.org/10.4049/jimmunol.2001152.
[136] T.H. Mayi, M. Daoudi, B. Derudas, B. Gross, G. Bories, K. Wouters, et al., Human adipose tissue macrophages display activation of cancer-related pathways, J. Biol. Chem. 287 (2012) 21904–21913, https://doi.org/10.1074/jbc.M111.315200.
[137] N.L. Springer, N.M. Iyengar, R. Bareja, A. Verma, M.S. Jochelson, D.D. Giri, et al., Obesity-associated extracellular matrix remodeling promotes a macrophage phenotype similar to tumor-associated macrophages, Am. J. Pathol. 189 (2019) 2019–2035, https://doi.org/10.1016/j.ajpath.2019.06.005.
[138] A. Labernadie, T. Kato, A. Brugues, X. Serra-Picamal, S. Derzsi, E. Arwert, et al., A mechanically active heterotypic E-cadherin/N-cadherin adhesion enables fibroblasts to drive cancer cell invasion, Nat. Cell Biol. 19 (2017) 224–237, https://doi.org/10.1038/ncb3478.
[139] E. Sahai, I. Astsaturov, E. Cukierman, D.G. DeNardo, M. Egeblad, R.M. Evans, et al., A framework for advancing our understanding of cancer-associated fibroblasts, Nat. Rev. Cancer 20 (2020) 174–186, https://doi.org/10.1038/s41568-019-0238-1.
[140] Y. Miyazaki, T. Oda, Y. Inagaki, H. Kushige, Y. Saito, N. Mori, et al., Adipose-derived mesenchymal stem cells differentiate into heterogeneous cancer-associated fibroblasts in a stroma-rich xenograft model, Sci. Rep. 11 (2021) 4690, https://doi.org/10.1038/s41598-021-84058-3.
[141] A.L. Strong, D.T. Pei, C.G. Hurst, J.M. Gimble, M.E. Burow, B.A. Bunnell, Obesity enhances the conversion of adipose-derived stromal/stem cells into carcinoma-associated fibroblast leading to cancer cell proliferation and progression to an invasive phenotype, Stem Cells Int 2017 (2017) 9216502, https://doi.org/10.1155/2017/9216502.
[142] M. Zaoui, M. Morel, N. Ferrand, S. Fellahi, J.P. Bastard, A. Lamaziere, et al., Breast-associated adipocytes secretome induce fatty acid uptake and invasiveness in breast cancer cells via CD36 independently of body mass index, menopausal status and mammary density, Cancers 11 (2019), https://doi.org/10.3390/cancers11122012.
[143] J. Xiong, H. Kawagishi, Y. Yan, J. Liu, Q.S. Wells, L.R. Edmunds, et al., A metabolic basis for endothelial-to-mesenchymal transition, e687, Mol. Cell 69 (2018) 689–698, https://doi.org/10.1016/j.molcel.2018.01.010.
[144] A. Santi, A. Caselli, F. Ranaldi, P. Paoli, C. Mugnaioni, E. Michelucci, et al., Cancer associated fibroblasts transfer lipids and proteins to cancer cells through cargo vesicles supporting tumor growth, Biochim. Biophys. Acta 1853 (2015) 3211–3223, https://doi.org/10.1016/j.bbamcr.2015.09.013.
[145] F. Lopes-Coelho, S. Andre, A. Felix, J. Serpa, Breast cancer metabolic cross-talk: fibroblasts are hubs and breast cancer cells are gatherers of lipids, Mol. Cell Endocrinol. 462 (2018) 93–106, https://doi.org/10.1016/j.mce.2017.01.031.
[146] J. Gong, Y. Lin, H. Zhang, C. Liu, Z. Cheng, X. Yang, et al., Reprogramming of lipid metabolism in cancer-associated fibroblasts potentiates migration of colorectal cancer cells, Cell Death Dis. 11 (2020) 267, https://doi.org/10.1038/s41419-020-2434-z.
[147] M.V. Apte, J.S. Wilson, A. Lugea, S.J. Pandol, A starring role for stellate cells in the pancreatic cancer microenvironment, Gastroenterology 144 (2013) 1210–1219, https://doi.org/10.1053/j.gastro.2012.11.037.
[148] F.R. Auciello, V. Bulusu, C. Oon, J. Tait-Mulder, M. Berry, S. Bhattacharyya, et al., A stromal lysolipid-autotaxin signaling axis promotes pancreatic tumor progression, Cancer Disco 9 (2019) 617–627, https://doi.org/10.1158/2159-8290.CD-18-1212.
[149] Z. Dagher, N. Ruderman, K. Tornheim, Y. Ido, Acute regulation of fatty acid oxidation and amp-activated protein kinase in human umbilical vein endothelial cells, Circ. Res 88 (2001) 1276–1282, https://doi.org/10.1161/hh1201.092998.
[150] S. Schoors, U. Bruning, R. Missiaen, K.C. Queiroz, G. Borgers, I. Elia, et al., Fatty acid carbon is essential for dNTP synthesis in endothelial cells, Nature 520 (2015) 192–197, https://doi.org/10.1038/nature14362.
[151] S.I. Yamagishi, D. Edelstein, X.L. Du, Y. Kaneda, M. Guzman, M. Brownlee, Leptin induces mitochondrial superoxide production and monocyte chemoattractant protein-1 expression in aortic endothelial cells by increasing fatty acid oxidation via protein kinase A, J. Biol. Chem. 276 (2001) 25096–25100, https://doi.org/10.1074/jbc.M007383200.
[152] X. Li, X. Sun, P. Carmeliet, Hallmarks of endothelial cell metabolism in health and disease, Cell Metab. 30 (2019) 414–433, https://doi.org/10.1016/j.cmet.2019.08.011.
[153] S. Schoors, K. De Bock, A.R. Cantelmo, M. Georgiadou, B. Ghesquiere, S. Cauwenberghs, et al., Partial and transient reduction of glycolysis by PFKFB3 blockade reduces pathological angiogenesis, Cell Metab. 19 (2014) 37–48, https://doi.org/10.1016/j.cmet.2013.11.008.
[154] H. Elmasri, C. Karaaslan, Y. Teper, E. Ghelfi, M. Weng, T.A. Ince, et al., Fatty acid binding protein 4 is a target of VEGF and a regulator of cell proliferation in

endothelial cells, FASEB J. 23 (2009) 3865–3873, https://doi.org/10.1096/fj.09-134882.
[155] C.E. Hagberg, A. Falkevall, X. Wang, E. Larsson, J. Huusko, I. Nilsson, et al., Vascular endothelial growth factor B controls endothelial fatty acid uptake, Nature 464 (2010) 917–921, https://doi.org/10.1038/nature08945.
[156] D.K. Glatzel, A. Koeberle, H. Pein, K. Loser, A. Stark, N. Keksel, et al., Acetyl-CoA carboxylase 1 regulates endothelial cell migration by shifting the phospholipid composition, J. Lipid Res 59 (2018) 298–311, https://doi.org/10.1194/jlr.M080101.
[157] U. Bruning, F. Morales-Rodriguez, J. Kalucka, J. Goveia, F. Taverna, K.C. S. Queiroz, et al., Impairment of angiogenesis by fatty acid synthase inhibition involves mTOR malonylation, e815, Cell Metab. 28 (2018) 866–880, https://doi.org/10.1016/j.cmet.2018.07.019.
[158] K.R. Solomon, K. Pelton, K. Boucher, J. Joo, C. Tully, D. Zurakowski, et al., Ezetimibe is an inhibitor of tumor angiogenesis, Am. J. Pathol. 174 (2009) 1017–1026, https://doi.org/10.2353/ajpath.2009.080551.
[159] K. Miura, H. Ohnishi, N. Morimoto, S. Minami, M. Ishioka, S. Watanabe, et al., Ezetimibe suppresses development of liver tumors by inhibiting angiogenesis in mice fed a high-fat diet, Cancer Sci. 110 (2019) 771–783, https://doi.org/10.1111/cas.13902.
[160] L. Fang, S.H. Choi, J.S. Baek, C. Liu, F. Almazan, F. Ulrich, et al., Control of angiogenesis by AIBP-mediated cholesterol efflux, Nature 498 (2013) 118–122, https://doi.org/10.1038/nature12166.
[161] A. Noghero, A. Perino, G. Seano, E. Saglio, G. Lo Sasso, F. Veglio, et al., Liver X receptor activation reduces angiogenesis by impairing lipid raft localization and signaling of vascular endothelial growth factor receptor-2, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 2280–2288, https://doi.org/10.1161/ATVBAHA.112.250621.
[162] C. Moessinger, I. Nilsson, L. Muhl, M. Zeitelhofer, B. Heller Sahlgren, J. Skogsberg, et al., VEGF-B signaling impairs endothelial glucose transcytosis by decreasing membrane cholesterol content, EMBO Rep. 21 (2020), e49343, https://doi.org/10.15252/embr.201949343.
[163] A.C. Daquinag, Z. Gao, C. Fussell, L. Immaraj, R. Pasqualini, W. Arap, et al., Fatty acid mobilization from adipose tissue is mediated by CD36 posttranslational modifications and intracellular trafficking, JCI Insight 6 (2021), https://doi.org/10.1172/jci.insight.147057.
[164] N.S. Pellegata, M. Berriel Diaz, M. Rohm, S. Herzig, Obesity and cancer-extracellular matrix, angiogenesis, and adrenergic signaling as unusual suspects linking the two diseases, Cancer Metastas. Rev. 41 (2022) 517–547, https://doi.org/10.1007/s10555-022-10058-y.
[165] D.Y. Kim, J.A. Park, Y. Kim, M. Noh, S. Park, E. Lie, et al., SALM4 regulates angiogenic functions in endothelial cells through VEGFR2 phosphorylation at Tyr1175, FASEB J. 33 (2019) 9842–9857, https://doi.org/10.1096/fj.201802516RR.
[166] D. Padua, X.H. Zhang, Q. Wang, C. Nadal, W.L. Gerald, R.R. Gomis, et al., TGFbeta primes breast tumors for lung metastasis seeding through angiopoietin-like 4, Cell 133 (2008) 66–77, https://doi.org/10.1016/j.cell.2008.01.046.
[167] L. Bougaret, L. Delort, H. Billard, C. Lequeux, N. Goncalves-Mendes, A. Mojallal, et al., Supernatants of adipocytes from obese versus normal weight women and breast cancer cells: in vitro impact on angiogenesis, J. Cell Physiol. 232 (2017) 1808–1816, https://doi.org/10.1002/jcp.25701.
[168] B.L. Ecker, J.Y. Lee, C.J. Sterner, A.C. Solomon, D.K. Pant, F. Shen, et al., Impact of obesity on breast cancer recurrence and minimal residual disease, Breast Cancer Res 21 (2019) 41, https://doi.org/10.1186/s13058-018-1087-7.
[169] K.B. Park, E.Y. Kim, H. Chin, D.J. Yoon, K.H. Jun, Leptin stimulates migration and invasion and maintains cancer stem-like properties in gastric cancer cells, Oncol. Rep. 48 (2022), https://doi.org/10.3892/or.2022.8377.
[170] Y. Hisano, T. Hla, Bioactive lysolipids in cancer and angiogenesis, Pharm. Ther. 193 (2019) 91–98, https://doi.org/10.1016/j.pharmthera.2018.07.006.
[171] M.G. Muoio, M. Talia, R. Lappano, A.H. Sims, V. Vella, F. Cirillo, et al., Activation of the S100A7/RAGE pathway by IGF-1 contributes to angiogenesis in breast cancer, Cancers 13 (2021), https://doi.org/10.3390/cancers13040621.
[172] A.E. Ringel, J.M. Drijvers, G.J. Baker, A. Catozzi, J.C. Garcia-Canaveras, B. M. Gassaway, et al., Obesity shapes metabolism in the tumor microenvironment to suppress anti-tumor immunity, e1826, Cell 183 (2020) 1848–1866, https://doi.org/10.1016/j.cell.2020.11.009.
[173] C. Zhang, C. Yue, A. Herrmann, J. Song, C. Egelston, T. Wang, et al., STAT3 activation-induced fatty acid oxidation in CD8(+) T effector cells is critical for obesity-promoted breast tumor growth, e145, Cell Metab. 31 (2020) 148–161, https://doi.org/10.1016/j.cmet.2019.10.013.
[174] S. Xu, O. Chaudhary, P. Rodriguez-Morales, X. Sun, D. Chen, R. Zappasodi, et al., Uptake of oxidized lipids by the scavenger receptor CD36 promotes lipid peroxidation and dysfunction in CD8(+) T cells in tumors, e1567, Immunity 54 (2021) 1561–1577, https://doi.org/10.1016/j.immuni.2021.05.003.
[175] E.D. Parker, A.R. Folsom, Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study, Int J. Obes. Relat. Metab. Disord. 27 (2003) 1447–1452, https://doi.org/10.1038/sj.ijo.0802437.
[176] A. Lazzati, S. Epaud, M. Ortala, S. Katsahian, E. Lanoy, Effect of bariatric surgery on cancer risk: results from an emulated target trial using population-based data, Br. J. Surg. 109 (2022) 433–438, https://doi.org/10.1093/bjs/znac003.
[177] L. Garcia-Estevez, J. Cortes, S. Perez, I. Calvo, I. Gallegos, G. Moreno-Bueno, Obesity and breast cancer: a paradoxical and controversial relationship influenced by menopausal status, Front Oncol. 11 (2021), 705911, https://doi.org/10.3389/fonc.2021.705911.
[178] S. Brandhorst, I.Y. Choi, M. Wei, C.W. Cheng, S. Sedrakyan, G. Navarrete, et al., A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan, Cell Metab. 22 (2015) 86–99, https://doi.org/10.1016/j.cmet.2015.05.012.
[179] M. Alidadi, M. Banach, P.C. Guest, S. Bo, T. Jamialahmadi, A. Sahebkar, The effect of caloric restriction and fasting on cancer, Semin Cancer Biol. 73 (2021) 30–44, https://doi.org/10.1016/j.semcancer.2020.09.010.
[180] N.F. Boyd, J. Stone, K.N. Vogt, B.S. Connelly, L.J. Martin, S. Minkin, Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature, Br. J. Cancer 89 (2003) 1672–1685, https://doi.org/10.1038/sj.bjc.6601314.
[181] M. Saadatian-Elahi, T. Norat, J. Goudable, E. Riboli, Biomarkers of dietary fatty acid intake and the risk of breast cancer: a meta-analysis, Int J. Cancer 111 (2004) 584–591, https://doi.org/10.1002/ijc.20284.
[182] B. Yang, X.L. Ren, Y.Q. Fu, J.L. Gao, D. Li, Ratio of n-3/n-6 PUFAs and risk of breast cancer: a meta-analysis of 274135 adult females from 11 independent prospective studies, BMC Cancer 14 (2014) 105, https://doi.org/10.1186/1471-2407-14-105.
[183] J.S. Zheng, X.J. Hu, Y.M. Zhao, J. Yang, D. Li, Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies, BMJ 346 (2013) f3706, https://doi.org/10.1136/bmj.f3706.
[184] A.P. Simopoulos, The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases, Exp. Biol. Med. 233 (2008) 674–688, https://doi.org/10.3181/0711-MR-311.
[185] V. Chajes, G. Torres-Mejia, C. Biessy, C. Ortega-Olvera, A. Angeles-Llerenas, P. Ferrari, et al., omega-3 and omega-6 Polyunsaturated fatty acid intakes and the risk of breast cancer in Mexican women: impact of obesity status, Cancer Epidemiol. Biomark. Prev. 21 (2012) 319–326, https://doi.org/10.1158/1055-9965.EPI-11-0896.
[186] J. Liu, D.W. Ma, The role of n-3 polyunsaturated fatty acids in the prevention and treatment of breast cancer, Nutrients 6 (2014) 5184–5223, https://doi.org/10.3390/nu6115184.
[187] J. Lopez-Moreno, G.M. Quintana-Navarro, J. Delgado-Lista, A. Garcia-Rios, J. F. Alcala-Diaz, F. Gomez-Delgado, et al., Mediterranean diet supplemented with coenzyme Q10 modulates the postprandial metabolism of advanced glycation end products in elderly men and women, J. Gerontol. A Biol. Sci. Med Sci. 73 (2018) 340–346, https://doi.org/10.1093/gerona/glw214.
[188] B.D. Hopkins, C. Pauli, X. Du, D.G. Wang, X. Li, D. Wu, et al., Suppression of insulin feedback enhances the efficacy of PI3K inhibitors, Nature 560 (2018) 499–503, https://doi.org/10.1038/s41586-018-0343-4.
[189] R.T. Martuscello, V. Vedam-Mai, D.J. McCarthy, M.E. Schmoll, M.A. Jundi, C. D. Louviere, et al., A supplemented high-fat low-carbohydrate diet for the treatment of glioblastoma, Clin. Cancer Res 22 (2016) 2482–2495, https://doi.org/10.1158/1078-0432.CCR-15-0916.
[190] P. Mukherjee, Z.M. Augur, M. Li, C. Hill, B. Greenwood, M.A. Domin, et al., Therapeutic benefit of combining calorie-restricted ketogenic diet and glutamine targeting in late-stage experimental glioblastoma, Commun. Biol. 2 (2019) 200, https://doi.org/10.1038/s42003-019-0455-x.
[191] A.E. Huerta, P.L. Prieto-Hontoria, M. Fernandez-Galilea, X. Escote, J.A. Martinez, M.J. Moreno-Aliaga, Effects of dietary supplementation with EPA and/or alpha-lipoic acid on adipose tissue transcriptomic profile of healthy overweight/obese women following a hypocaloric diet, Biofactors 43 (2017) 117–131, https://doi.org/10.1002/biof.1317.
[192] L.P. Fernandez, M. Gomez de Cedron, A. Ramirez de Molina, Alterations of lipid metabolism in cancer: implications in prognosis and treatment, Front Oncol. 10 (2020), 577420, https://doi.org/10.3389/fonc.2020.577420.
[193] C. Carpene, S. Gomez-Zorita, S. Deleruyelle, M.A. Carpene, Novel strategies for preventing diabetes and obesity complications with natural polyphenols, Curr. Med Chem. 22 (2015) 150–164, https://doi.org/10.2174/0929867321666140815124052.
[194] T. Ni, Z. He, Y. Dai, J. Yao, Q. Guo, L. Wei, Oroxylin A suppresses the development and growth of colorectal cancer through reprogram of HIF1alpha-modulated fatty acid metabolism, Cell Death Dis. 8 (2017), e2865, https://doi.org/10.1038/cddis.2017.261.
[195] P. Louis, G.L. Hold, H.J. Flint, The gut microbiota, bacterial metabolites and colorectal cancer, Nat. Rev. Microbiol 12 (2014) 661–672, https://doi.org/10.1038/nrmicro3344.
[196] A.M. Sheflin, A.K. Whitney, T.L. Weir, Cancer-promoting effects of microbial dysbiosis, Curr. Oncol. Rep. 16 (2014) 406, https://doi.org/10.1007/s11912-014-0406-0.
[197] B. Batchuluun, S.L. Pinkosky, G.R. Steinberg, Lipogenesis inhibitors: therapeutic opportunities and challenges, Nat. Rev. Drug Disco 21 (2022) 283–305, https://doi.org/10.1038/s41573-021-00367-2.
[198] J.A. Menendez, L. Vellon, R. Colomer, R. Lupu, Pharmacological and small interference RNA-mediated inhibition of breast cancer-associated fatty acid synthase (oncogenic antigen-519) synergistically enhances Taxol (paclitaxel)-induced cytotoxicity, Int J. Cancer 115 (2005) 19–35, https://doi.org/10.1002/ijc.20754.
[199] G. Falchook, J. Infante, H.T. Arkenau, M.R. Patel, E. Dean, E. Borazanci, et al., First-in-human study of the safety, pharmacokinetics, and pharmacodynamics of first-in-class fatty acid synthase inhibitor TVB-2640 alone and with a taxane in advanced tumors, EClinicalMedicine 34 (2021), 100797, https://doi.org/10.1016/j.eclinm.2021.100797.
[200] F. Hossain, A.A. Al-Khami, D. Wyczechowska, C. Hernandez, L. Zheng, K. Reiss, et al., Inhibition of fatty acid oxidation modulates immunosuppressive functions of myeloid-derived suppressor cells and enhances cancer therapies, Cancer Immunol. Res 3 (2015) 1236–1247, https://doi.org/10.1158/2326-6066.CIR-15-0036.

[201] R. Camarda, A.Y. Zhou, R.A. Kohnz, S. Balakrishnan, C. Mahieu, B. Anderton, et al., Inhibition of fatty acid oxidation as a therapy for MYC-overexpressing triple-negative breast cancer, Nat. Med 22 (2016) 427–432, https://doi.org/10.1038/nm.4055.
[202] M.J. Watt, A.K. Clark, L.A. Selth, V.R. Haynes, N. Lister, R. Rebello, et al., Suppressing fatty acid uptake has therapeutic effects in preclinical models of prostate cancer, Sci. Transl. Med. 11 (2019), https://doi.org/10.1126/scitranslmed.aau5758.
[203] G. Pascual, A. Avgustinova, S. Mejetta, M. Martin, A. Castellanos, C.S. Attolini, et al., Targeting metastasis-initiating cells through the fatty acid receptor CD36, Nature 541 (2017) 41–45, https://doi.org/10.1038/nature20791.
[204] J. Zhao, Z. Zhi, C. Wang, H. Xing, G. Song, X. Yu, et al., Exogenous lipids promote the growth of breast cancer cells via CD36, Oncol. Rep. 38 (2017) 2105–2115, https://doi.org/10.3892/or.2017.5864.
[205] C.D. Fryar, T.C. Chen, X. Li, Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999-2010, NCHS Data Brief. (2012) 1–8.
[206] W.R. Farwell, R.E. Scranton, E.V. Lawler, R.A. Lew, M.T. Brophy, L.D. Fiore, et al., The association between statins and cancer incidence in a veterans population, J. Natl. Cancer Inst. 100 (2008) 134–139, https://doi.org/10.1093/jnci/djm286.
[207] S.F. Nielsen, B.G. Nordestgaard, S.E. Bojesen, Statin use and reduced cancer-related mortality, N. Engl. J. Med. 367 (2012) 1792–1802, https://doi.org/10.1056/NEJMoa1201735.
[208] J. Longo, J.E. van Leeuwen, M. Elbaz, E. Branchard, L.Z. Penn, Statins as anticancer agents in the era of precision medicine, Clin. Cancer Res. 26 (2020) 5791–5800, https://doi.org/10.1158/1078-0432.CCR-20-1967.
[209] M. Roy, H.J. Kung, P.M. Ghosh, Statins and prostate cancer: role of cholesterol inhibition vs. prevention of small GTP-binding proteins, Am. J. Cancer Res 1 (2011) 542–561.
[210] M. Cejuela, B. Martin-Castillo, J.A. Menendez, S. Pernas, Metformin and breast cancer: where are we now, Int J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms23052705.
[211] K. Zhang, P. Bai, H. Dai, Z. Deng, Metformin and risk of cancer among patients with type 2 diabetes mellitus: a systematic review and meta-analysis, Prim. Care Diabetes 15 (2021) 52–58, https://doi.org/10.1016/j.pcd.2020.06.001.
[212] H. Guo, W. Kong, L. Zhang, J. Han, L.H. Clark, Y. Yin, et al., Reversal of obesity-driven aggressiveness of endometrial cancer by metformin, Am. J. Cancer Res 9 (2019) 2170–2193.
[213] R.A. Hampsch, J.D. Wells, N.A. Traphagen, C.F. McCleery, J.L. Fields, K. Shee, et al., AMPK activation by metformin promotes survival of dormant ER(+) breast cancer cells, Clin. Cancer Res 26 (2020) 3707–3719, https://doi.org/10.1158/1078-0432.CCR-20-0269.
[214] D. Lettieri Barbato, R. Vegliante, E. Desideri, M.R. Ciriolo, Managing lipid metabolism in proliferating cells: new perspective for metformin usage in cancer therapy, Biochim Biophys. Acta 1845 (2014) 317–324, https://doi.org/10.1016/j.bbcan.2014.02.003.
[215] T.A. Smith, S.M. Phyu, Metformin decouples phospholipid metabolism in breast cancer cells, PLoS One 11 (2016), e0151179, https://doi.org/10.1371/journal.pone.0151179.
[216] Y. Lu, A. Hajjar, V.L. Cryns, A. Trentham-Dietz, R.E. Gangnon, B.M. Heckman-Stoddard, et al., Breast cancer risk for women with diabetes and the impact of metformin: a meta-analysis, Cancer Med (2022), https://doi.org/10.1002/cam4.5545.
[217] A.A. El-Attar, O.M. Ibrahim, S.A. Alhassanin, E.S. Essa, T.M. Mostafa, Effect of metformin as an adjuvant therapy to letrozole on estradiol and other biomarkers involved in the pathogenesis of breast cancer in overweight and obese postmenopausal women: a pilot study, Eur. J. Clin. Pharm. 79 (2023) 299–309, https://doi.org/10.1007/s00228-022-03444-6.
[218] P.J. Goodwin, B.E. Chen, K.A. Gelmon, T.J. Whelan, M. Ennis, J. Lemieux, et al., Effect of metformin vs placebo on invasive disease-free survival in patients with breast cancer: the MA.32 randomized clinical trial, JAMA 327 (2022) 1963–1973, https://doi.org/10.1001/jama.2022.6147.
[219] H.W. Lin, C.H. Tseng, A review on the relationship between SGLT2 inhibitors and cancer, Int J. Endocrinol. 2014 (2014), 719578, https://doi.org/10.1155/2014/719578.
[220] K. Kaji, N. Nishimura, K. Seki, S. Sato, S. Saikawa, K. Nakanishi, et al., Sodium glucose cotransporter 2 inhibitor canagliflozin attenuates liver cancer cell growth and angiogenic activity by inhibiting glucose uptake, Int J. Cancer 142 (2018) 1712–1722, https://doi.org/10.1002/ijc.31193.
[221] S.G. Eliaa, A.A. Al-Karmalawy, R.M. Saleh, M.F. Elshal, Empagliflozin and doxorubicin synergistically inhibit the survival of triple-negative breast cancer cells via interfering with the mTOR Pathway and inhibition of calmodulin: in vitro and molecular docking studies, ACS Pharm. Transl. Sci. 3 (2020) 1330–1338, https://doi.org/10.1021/acsptsci.0c00144.
[222] A.R. Nasiri, M.R. Rodrigues, Z. Li, B.P. Leitner, R.J. Perry, SGLT2 inhibition slows tumor growth in mice by reversing hyperinsulinemia, Cancer Metab. 7 (2019) 10, https://doi.org/10.1186/s40170-019-0203-1.
[223] M. Dutka, R. Bobinski, T. Francuz, W. Garczorz, K. Zimmer, T. Ilczak, et al., SGLT-2 inhibitors in cancer treatment-mechanisms of action and emerging new perspectives, Cancers 14 (2022), https://doi.org/10.3390/cancers14235811.