Progress in Lipid Research 80 (2020) 101055

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

Lipids in the tumor microenvironment: From cancer progression to treatment

Kevin C. Corn[a], McKenzie A. Windham[a], Marjan Rafat[a,b,c,*]

[a] Department of Chemical and Biomolecular Engineering, Vanderbilt University, Nashville, TN, USA
[b] Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA
[c] Department of Radiation Oncology, Vanderbilt University Medical Center, Nashville, TN, USA

ARTICLE INFO

Keywords:
Lipid Metabolism
Lipid Signaling
Tumor Microenvironment
Immune Response
Radiation Therapy
Metastasis

ABSTRACT

Over the past decade, the study of metabolic abnormalities in cancer cells has risen dramatically. Cancer cells can thrive in challenging environments, be it the hypoxic and nutrient-deplete tumor microenvironment or a distant tissue following metastasis. The ways in which cancer cells utilize lipids are often influenced by the complex interactions within the tumor microenvironment and adjacent stroma. Adipocytes can be activated by cancer cells to lipolyze their triglyceride stores, delivering secreted fatty acids to cancer cells for uptake through numerous fatty acid transporters. Cancer-associated fibroblasts are also implicated in lipid secretion for cancer cell catabolism and lipid signaling leading to activation of mitogenic and migratory pathways. As these cancer-stromal interactions are exacerbated during tumor progression, fatty acids secreted into the microenvironment can impact infiltrating immune cell function and phenotype. Lipid metabolic abnormalities such as increased fatty acid oxidation and *de novo* lipid synthesis can provide survival advantages for the tumor to resist chemotherapeutic and radiation treatments and alleviate cellular stresses involved in the metastatic cascade. In this review, we highlight recent literature that demonstrates how lipids can shape each part of the cancer lifecycle and show that there is significant potential for therapeutic intervention surrounding lipid metabolic and signaling pathways.

1. Introduction

Since Otto Warburg's initial observation that cancer cells metabolize glucose in a manner different from their normal-tissue counterparts, it has been known that cancer cells have a unique metabolic profile [1–3]. The metabolic requirements of cells as they develop from benign outgrowths to malignant and invasive cancerous lesions are complex and dynamic. With uncontrolled proliferation, cancer cells require an extensive production of biomolecules to generate the building blocks of new sister cells. Available metabolites change as they invade into the surrounding stromal tissue and interact with new cell types. Angiogenesis increases the delivery of nutrients and oxygen to the tumor during growth; however, most tumors develop nutrient-poor and hypoxic regions that demand cancer cells adapt their metabolic profiles to survive. As cancer cells find their way into the circulatory or lymphatic system and eventually colonize a distant tissue, they will face a host of new metabolic challenges in the vastly different stromal landscape. To combat cancer at any of these stages, researchers must develop therapeutic strategies that exploit these unique metabolic profiles while ensuring those treatments do not significantly harm the surrounding normal tissue. It is therefore no surprise that metabolic reprogramming of cancer cells has been at the forefront of cancer

Abbreviations: ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; ATX, autotaxin; CAF, cancer-associated fibroblast; CPT, carnitine palmitoyltransferase; CT, chemotherapy; CTC, circulating tumor cell; DC, dendritic cell; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; FABP, fatty acid binding protein; FAO, fatty acid oxidation; FASN, fatty acid synthase; FATP, fatty acid transport protein; FFA, free fatty acid; HER2, human epidermal growth factor 2; HIF, hypoxia inducible factor; IFN, interferon; IL, interleukin; LD, lipid droplet; LPA, lysophosphatidic acid; LPAR, lysophosphatidic acid receptor; LPC, lysophosphatidylcholine; LPL, lipoprotein lipase; MSR, macrophage scavenger receptor; NK, natural killer cell; PDAC, pancreatic ductal adenocarcinoma; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cell; PPAR, peroxisome proliferator-activated receptor; PPP, pentose phosphate pathway; ROS, reactive oxygen species; RT, radiation therapy; SCD, stearoyl-CoA desaturase; TAM, tumor-associated macrophage; TCA, tricarboxylic acid; Teff, CD8+ effector T cell; Th1, CD4+ T-helper 1 cell; Th17, CD4+ T-helper 17 cell; Th2, CD4+ T-helper 2 cell; TIL, tumor infiltrating lymphocyte; TLR, toll-like receptor; TME, tumor microenvironment; Treg, regulatory T cell; UPR, unfolded protein response; VLDL, very low density lipoprotein; XBP, X-box binding protein

* Corresponding author at: Vanderbilt University, Engineering and Science Building, Rm. 426, Nashville, TN 37212.
E-mail address: marjan.rafat@vanderbilt.edu (M. Rafat).

https://doi.org/10.1016/j.plipres.2020.101055
Received 15 June 2020; Received in revised form 5 August 2020; Accepted 7 August 2020
Available online 11 August 2020
0163-7827/

research within the past decade [4].

Understanding the interplay between lipids, their metabolism, and related signaling is critical. Lipids not only comprise a diverse set of biomolecules with varying compositions and functions, ranging from fatty acyls, glycerophospholipids, and sphingolipids to sterol and prenol lipids, but they also play a ubiquitous role in cancer – they make up the physical barriers of cellular organelles and protect the cell from its extracellular space, they can be utilized as substrates for biomass production [5,6] or stored for future oxidation to produce energy for cell movement and proliferation [7–9], and they can directly bind to receptors to initiate complex signaling pathways that promote cell growth and migration [10–12]. Excessive accumulation of lipids or a shift in saturated and unsaturated fatty acid levels can disrupt homeostasis and enhance cellular stress. Changes in lipid metabolism and signaling, however, have only more recently been considered one of the hallmarks of aberrant cell growth and cancer progression. In cancer cells, the production of phospholipids for cell membranes is critical and must be balanced with other metabolic demands. Cancer cells can be influenced by circulating free fatty acids (FFAs) and other lipid molecules during stromal invasion, which can dramatically alter cell signaling or provide additional substrates for cell growth. These effects are even more important when considering microenvironmental changes as a result of obesity [13–15].

When exploring the impact of lipids within the tumor microenvironment (TME), not only cancer cells but also the entire population of immune and stromal cells must be considered. The cellular players and their interactions within the TME, just like the variations of cellular metabolism at each stage of cancer progression, are complex and dynamic (Fig. 1). Understanding how these cell types change the lipid metabolism of cancer cells, or how they can be influenced by lipids within the TME, is as important as examining the changes to cancer cells themselves for developing more effective treatments. In this review, we explore recent advances in how lipids impact the TME from cancer progression through treatment, recurrence, and metastasis. We highlight areas that should be further evaluated to improve treatment outcomes, enhance survival, and prevent further spread and progression after therapy.

2. Lipids within the tumor microenvironment facilitate cancer progression

Uncontrolled proliferation of cancer cells necessitates accumulation of a significant quantity of lipids to make up the membranes and organelles of these cells – these lipids can be acquired from exogenous sources or synthesized endogenously through lipogenic pathways. Additionally, as a cancer cell invades into the surrounding stroma, the degradation of the extracellular matrix (ECM) and migration along ECM fibers requires a significant source of ATP [16]. In this section, we focus on recent literature that evaluates these two sources of fatty acids and lipids for cancer cells and how tumors utilize these molecules. We also look at the unique role of lipids in the microenvironment beyond metabolic requirements. Fig. 2 illustrates how lipids within the TME impact cancer progression.

2.1. An exogenous supply of fatty acids

An important metabolic marker of cancer cells that has come under intense observation over the past several years relates to the ability of these cells to uptake fatty acids from their environment. This is especially true for cancers that develop in tissues containing or adjacent to large swaths of adipocytes and may be exacerbated in obesity, where there is generally an increase in the circulation of FFAs [14,15]. Breast cancer is a major area of study for the impact of exogenous lipids on tumor progression given the significant presence of adipocytes in breast tissue. Other cancers, including melanoma [17], gastric [18,19], ovarian [20,21], prostate [22], and colon cancers [7], are also influenced by interactions with surrounding adipose tissue. Many studies focus on the role of fatty acid translocase, or CD36, a membrane-bound glycoprotein and scavenger involved in delivering exogenous lipids into the cytoplasm of cells [23]; however, other proteins like the fatty acid transport proteins (FATPs) and fatty acid binding proteins (FABPs) are examined as well.

Breast cancer cells appear to exist in a parasitic relationship with adipocytes and their lipid stores. Co-culturing cancer cells with adipocytes results in the activation of lipolysis within adipocytes, releasing fatty acids into the extracellular space. Tracing studies show that these fatty acids are taken up by cancer cells, inducing an increase in both their proliferation and migration [24]. Breast cancer cells respond to adipocyte lipolysis with an increase in carnitine palmitoyltransferase 1A (CPT1A) expression, the rate-limiting enzyme of long-chain fatty acid transport into the mitochondria for fatty acid oxidation (FAO) [25,26]. Once adipocytes are activated by cancer cells, they will ultimately secrete higher levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) [27,28]. These pro-inflammatory cytokines are also secreted by cancer cells and contribute to inducing the release of fatty acids from adipocyte triglyceride stores as they are considered strong lipolytic factors [29,30]. However, Wang *et al.* showed that blocking IL-6 does not prevent lipolysis from occurring in adipocytes, indicating that many factors may be involved [26]. Upregulation of IL-6 may amplify the metabolic crosstalk between the two cell types as IL-6 signals through the STAT3 pathway and CD36 has recently been shown to be a downstream target of activated STAT3, which would further promote fatty acid uptake by cancer cells [31,32]. If this is the case, metabolically activated adipose tissue macrophages that also secrete high levels of IL-6 may play a role in this axis [33].

Another major adipokine implicated in the transfer of fatty acids from adipocytes to breast cancer cells is FABP4, which is typically found in the cytoplasm and involved in intracellular trafficking of fatty acids between organelles but can also be secreted. Contradictory results show that FABP4 is either taken up by cancer cells or just binds to phospholipids on the cell surface to induce signaling events. Regardless, exogenous FABP4 can induce expression of fatty acid transporters CD36 and FABP5 in breast cancer cells [34,35]. The role of FABP4 in cancer progression extends well beyond breast cancer as it has been identified in acute myeloid leukemia [36,37], non-small cell lung cancer [38], ovarian cancer [39], and oral squamous cell carcinoma [40].

Although cancer-associated fibroblasts (CAFs) are more frequently known to induce epithelial-mesenchymal transition (EMT) [41,42] and secrete immunosuppressive and pro-angiogenic factors in the TME [43,44], recent literature suggests they may influence lipid transfer and uptake. CAFs induce the upregulation of FATP1 in human MDA-MB-231 triple-negative breast cancer cells, resulting in an increase in exogenous fatty acid uptake from the TME [45]. CAFs can additionally transfer lipids to cancer cells through ectosomes, which have been demonstrated to increase cancer cell proliferation [46].

Dietary sources of lipids are yet another way in which cancer cells can acquire fatty acids. Utilizing these sources involves the expression of lipoprotein lipase (LPL) which hydrolyzes the triglyceride content in circulating very low density lipoproteins (VLDL). These fatty acids can then be taken up by CD36. Increased LPL expression and activity has been reported in non-small cell lung cancer [47], hepatocellular carcinoma [48], high grade glioma [49], and triple-negative breast cancer [50]. Recently, receptor-mediated endocytosis of intact VLDL, facilitated by LPL in a non-enzymatic fashion, was demonstrated as a new approach for lipid uptake in breast cancer cells. The endocytosis of these lipoproteins induced a shift in metabolism-related gene expression for increased lipid transport and lipid droplet (LD) formation proteins [51]. The combination of these studies suggests that targeting transport proteins involved in fatty acid uptake could be used to combat cancer progression; however, developing drugs to target these pathways may be challenging given the myriad of ways cells can utilize these resources from the extracellular space.

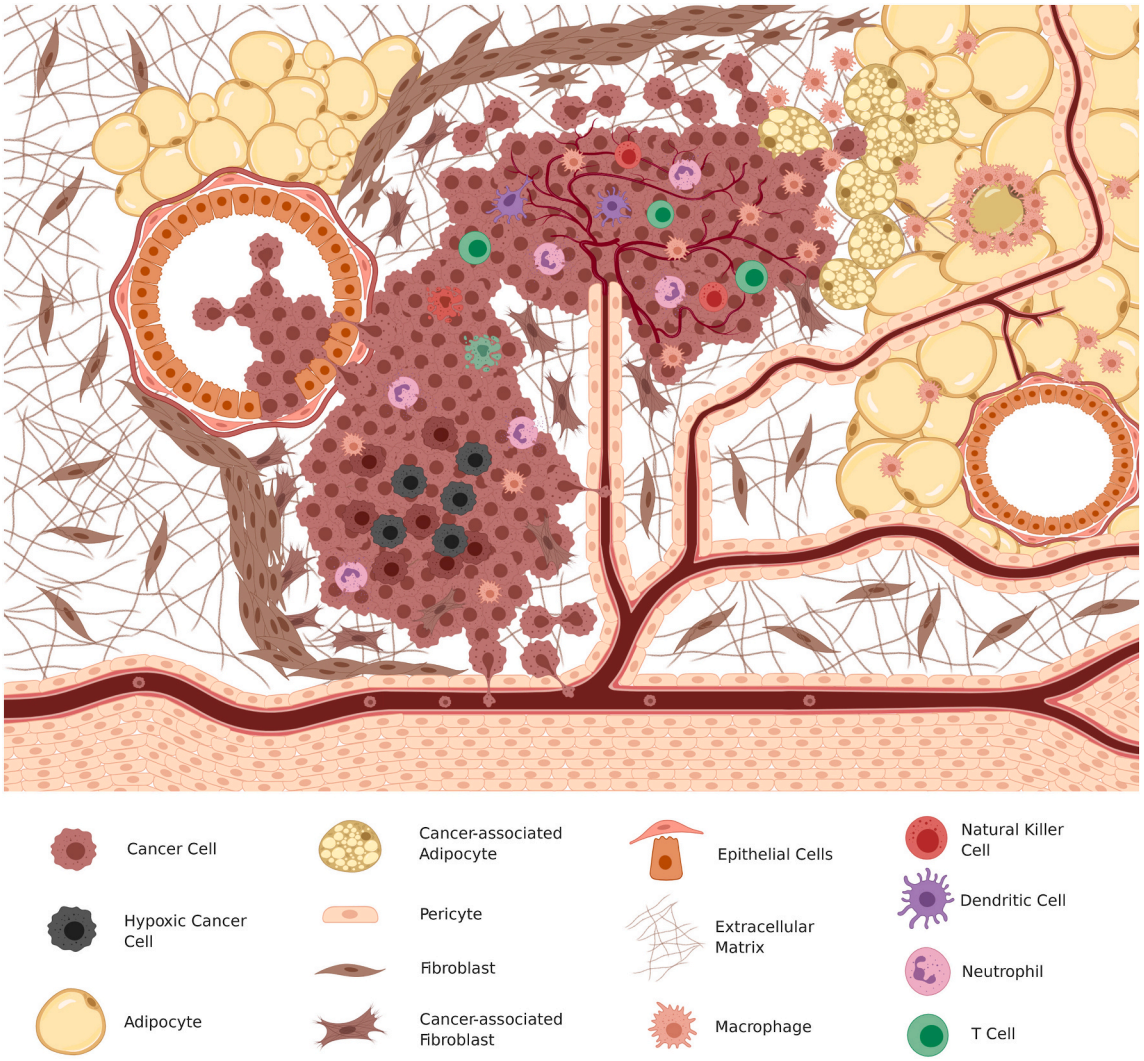

Fig. 1. Complex interactions within the tumor microenvironment (TME). The TME consists of a complex mixture of cancer cells, immune cells, and stromal cells. As cancer cells invade through the basement membrane and into the stromal compartment, they activate nearby stromal cells, such as adipocytes and fibroblasts, and influence lipid metabolism [24,26,29,30,45,46]. The recruitment of fibroblasts and immune cells can result in significant ECM deposition, which can restrict metabolites such as glucose and oxygen from diffusing into the core of the tumor [10]. Fatty acids secreted by tumor-associated stromal cells can have a tumor-promoting effect on many of the immune cells that are recruited to the TME, including macrophages, natural killer cells, dendritic cells, neutrophils, and T cells. The lipid metabolic reprogramming of tumor cells due to these interactions may provide survival advantages for cells in treatment and metastasis.

2.2. Synthesizing and utilizing fatty acids

Regardless of the concentration of circulating FFAs and their uptake, cancer cells have high levels of *de novo* lipogenesis [52–55], a unique characteristic considering most human tissues other than adipose tissue and the liver have very little lipid synthesis and low expression of fatty acid synthase (FASN) [56,57]. Newly synthesized fatty acids are used in the production of phospholipids for membranes and lipid rafts, in addition to essential polyunsaturated omega-3 and omega-6 fatty acids, which are acquired externally and cannot be synthesized *de novo* [58]. Some studies challenge where synthesized fatty acids ultimately are used by cancer cells, suggesting that *de novo* fatty acids are beyond the needs of cancer cell requirements and instead exogenous fatty acids are the source for membrane synthesis [5,6]. Both may be true and likely dependent upon conditions within the TME. FASN is responsible for combining malonyl-CoA and acetyl-CoA to produce the saturated fatty acid palmitate. High levels of synthesized palmitate are lipotoxic to cells, but oleate from external sources can mitigate palmitate-induced lipotoxicity [59]. The stearoyl-CoA desaturase 1 (SCD1) enzyme is involved in the formation of monounsaturated fatty acids, including oleate, and its increased expression has been shown to promote progression of several cancers [60–62]. The enzymatic activity of SCD1, however, requires oxygen, which may be scarce in the poorly vascularized and hypoxic TME. In this scenario, hypoxic cells may bypass lipid synthesis pathways and increase uptake of exogenous unsaturated fatty acids from lysophospholipids as opposed to free oleate [63]. Cells that develop mutations for increased fatty acid uptake and LD synthesis in normoxia can later utilize their reserves during hypoxia, releasing unsaturated fatty acids to balance saturation levels [64]. Beyond hypoxia, saturated and unsaturated fatty acids may influence migration and invasion of cancer cells. Higher levels of saturated fatty acids in membrane phospholipids increase the density and decrease the fluidity of the cell membrane. Cells that cannot uptake unsaturated fatty acids or synthesize them acquire a more rounded morphology which is associated with increased directional changes and lower migrational speed as a result of decreased membrane fluidity [65]. Conversely, failure of cells to synthesize saturated fatty acids interrupts lipid raft domains and interferes with invadopodia formation,

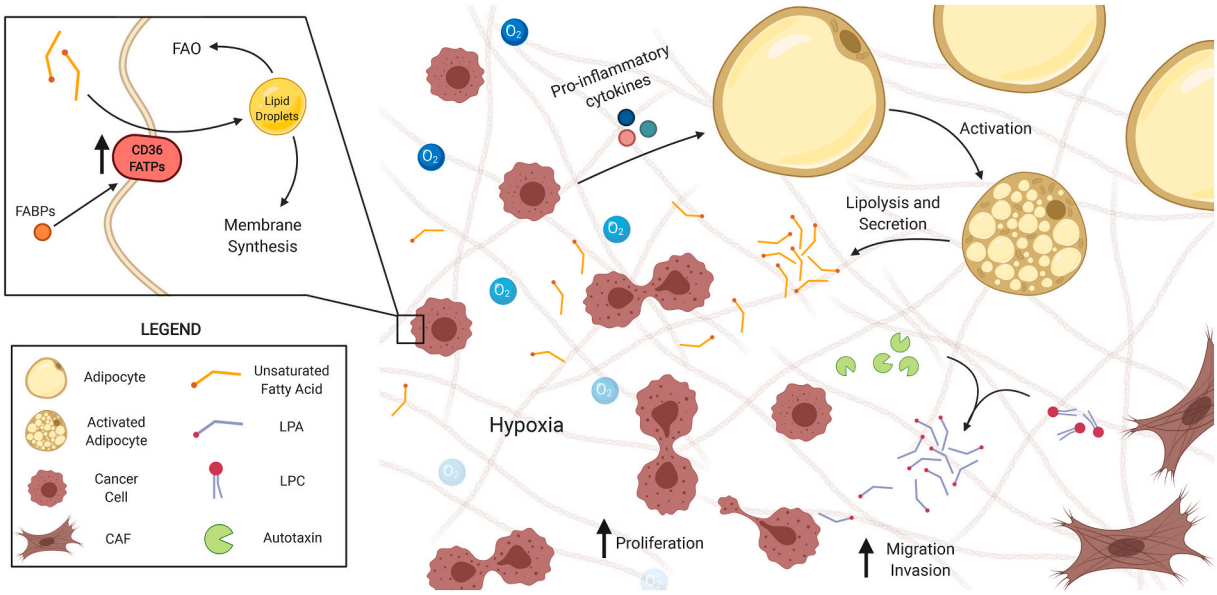

Fig. 2. Exogenous fatty acids from the TME promote cancer progression and survival. As cancer cells invade into the surrounding stroma, they come into contact with and activate stromal cells, including adipocytes and fibroblasts [24,45,46]. Activation of adipocytes, potentially by pro-inflammatory cytokines, induces lipolysis of stored triglycerides and secretion of fatty acids [24,26,29,30]. Adipokines such as FABP4 increase the expression of fatty acid transporters, including CD36, to facilitate the uptake of these fatty acids by cancer cells [34,35]. Unsaturated fatty acids that are acquired and stored in LDs provide benefits to cells during hypoxia, where *de novo* synthesis of unsaturated fatty acids is blocked [63,64]. Unsaturated fatty acids prevent lipotoxicity and allow for membrane synthesis with sufficient fluidity to promote tumor cell migration and invasion [65]. These fatty acids can also be utilized in FAO when oxygen levels are sufficient [7–9]. Activated CAFs and other stromal cells secrete LPC that is hydrolyzed from adipocyte- and cancer cell-secreted ATX to promote cancer cell migration, invasion, and proliferation [10–12].

decreasing cell invasion [66]. Taken together, maintaining a tight balance between saturated and unsaturated lipids is critical during cancer progression.

If not used for membrane synthesis, fatty acids synthesized and stored in LDs or taken up exogenously can be utilized for FAO to promote tumor growth [7–9]. Adipocytes have been implicated in this process and can secrete exosomes that contain proteins involved in β-oxidation, which can be taken up and utilized by melanoma cells without increasing mRNA levels for these enzymes [67]. In acute myeloid leukemia cells, bone marrow adipocytes induce FAO that reduces reactive oxygen species (ROS) and apoptosis [68]. While FAO is a highly efficient form of ATP generation for cancer cells, lipids can impact proliferation and migration in ways other than providing an energy source.

2.3. Lipids are more than just metabolites

Beyond utilization as the substrates for membrane synthesis and a high source of energy for cancer cells, lipids can play additional roles in the TME. In tumors that experience extreme desmoplasia, the dense ECM surrounding the tumor results in impediment of the local vasculature to deliver oxygen and metabolites, leaving the TME relatively nutrient-deficient. This occurs in pancreatic ductal adenocarcinoma (PDAC), where cancer cells scavenge lipid molecules from CAFs in the form of lysophosphatidylcholine (LPC) and its hydrolyzed product lysophosphatidic acid (LPA). PDAC cells can incorporate CAF-secreted LPC into newly synthesized membranes. However, CAF-secreted autotaxin (ATX) hydrolyzes LPC to LPA, which can serve as a mitogenic and migratory signaling molecule. When exploring the impact of this LPC-ATX-LPA axis *in vivo,* significant reduction of tumor growth is observed upon the inhibition of ATX when PDAC cells are co-injected with CAFs into the pancreas compared to injection of only PDAC cells. These results further highlight the importance of tumor-associated stromal cells in lipid-based tumor progression [10].

Pro-inflammatory cytokines secreted by tumor-associated stromal cells may induce ATX expression in cancer cells. In pancreatic neuroendocrine neoplasms, IL-6 has been shown to activate STAT3, which results in increased ATX expression [69]. Activated STAT3 has also been linked to increased ATX expression and enhanced migratory capacity in breast cancer cells [70]. While breast cancer is known to be highly influenced by the LPC-ATX-LPA axis, the stromal cells in the breast tissue microenvironment, such as the adipose-derived stem cells and adipocytes, produce the majority of ATX compared to breast cancer cells themselves. Secreted factors from cancer cells may further increase ATX expression in these stromal cells as these cell types express higher levels of ATX in patients with tumors compared to normal healthy breast adipose tissue [71]. The conversion of LPC to LPA by ATX and the resultant signaling appears to impact breast cancer proliferation at all stages of progression [11]. Volden and colleagues observed an increase in proliferation and a decrease in apoptosis at biologically relevant LPA concentrations in normal mammary epithelial, carcinoma *in situ*, and invasive estrogen-receptor negative cell lines. Of the three lines, normal epithelial cells secrete higher levels of ATX compared to the progressively more malignant cells, indicating a potential role in ATX and LPA in initial stages of *in situ* growth. LPC exposure causes the highest proliferation in the invasive cell lines despite lower ATX secretion, suggesting that this phospholipid may alter proliferation through other signaling cascades [12]. Regardless, ATX inhibition can reduce initial tumor growth in syngeneic models of triple-negative breast cancer. When the cells begin to invade into the surrounding tissue, ATX inhibition no longer has a significant effect on primary tumor growth; however, disrupting this LPC-ATX-LPA axis helps to reduce the number of metastatic nodules that form in the lungs [72].

The contributions of ATX, LPC, and LPA continue to be investigated as important metabolic and signaling molecules in several other cancers of various origins, including glioblastoma multiforme [73], renal cell and bladder carcinoma [74], thyroid cancer [75], colorectal cancer [76], and ovarian cancer [77]. Recent literature on the LPC-ATX-LPA axis and cancer progression has focused on how the six LPA receptors (LPARs) can play opposing roles in cancer cell migration, proliferation, and metastatic potential [78]. Increased migration is observed after LPA signaling through LPAR1 and LPAR2 in ovarian cancer [79] and

Table 1
Lipids and metabolic pathways influencing the immune response and tumor progression

Immune cell	Lipid species, protein, or metabolic pathway implicated	Impact on cancer progression	References
M1-like TAMs	Aerobic glycolysis	Pro-inflammatory response, tumor suppression	[89,90]
M2-like TAMs	Fatty acid uptake, CD36 expression, high rates of FAO	Immune suppression, pro-tumorigenic	[91–94,102]
		Promotion of tumor cell migration	[100]
		Cytokine secretion leading to recruitment of effector cells, anti-tumorigenic	[101]
		No effect on M2 polarization	[99]
	Lipoprotein hydrolysis	Immune suppression, pro-tumorigenic	[95,96]
CD8+ T Cells	High levels of FFAs	Inhibition of CD8+ Teff function, pro-tumorigenic	[104]
	FAO, moderate levels of FFAs	Promotion of CD8+ Teff function, anti-tumorigenic	[106,109,110]
	LPA signaling	Impaired CD8+ Teff function, pro-tumorigenic	[123,124]
Tregs	FFA uptake, CD36, FAO, fatty acid synthesis	Immune suppression, pro-tumorigenic	[111,114,116,117]
DCs	FABP4, MSR1, LPL, lipid accumulation, XBP1, ER stress	DC antigen presentation dysfunction, pro-tumorigenic	[126–130]
NK Cells	Aerobic glycolysis	Anti-tumorigenic, increased effector functions	[132]
	Exogenous fatty acid uptake	Deficient effector function, pro-tumorigenic	[134–137,139]
Neutrophils	FAO	T cell suppression, pro-tumorigenic	[144]
PMN-MDSCs	FATPs, lipid accumulation, FAO	T cell suppression, pro-tumorigenic	[149–152]

LPAR6 in pancreatic cancer [80]. Alternatively, cancer cell motility is decreased following LPA signaling through LPAR4 and LPAR6 in colon cancer [81], LPAR2 and LPAR5 in melanoma [82], and LPAR4 and LPAR5 in pancreatic cancer [80]. Although LPA signaling through LPAR5 decreases cell motility in melanoma, knockout of LPAR5 in mice decreases lung metastasis, suggesting the importance of this receptor on stromal or immune cells in preventing melanoma spread to other organs [82]. Future work will be necessary to establish the expression patterns of LPARs in various cancer types. Evaluation of the effects of LPA signaling on cancer cell motility and proliferation must also be paired with studying the effects on stromal cells to better understand how to target this lipid signaling axis for improving patient outcomes.

3. Lipid metabolism and the immune response to tumor progression

Cells of both innate and adaptive immunity can respond to a growing tumor and elicit a pro-inflammatory response to help eliminate the cancer cells or succumb to suppressive signals from the TME and ultimately help fuel tumor progression. Here, we discuss how the metabolic status of these immune cells and their usage of lipids within the TME can influence their function. A summary of the major lipid enzymes and pathways for each of the immune cell types is presented in Table 1.

3.1. Macrophages

Of all the immune cells that are recruited to the TME, macrophages can make upwards of half of the cell population in some cancers and have been implicated in every stage of cancer progression [83]. Infiltrating macrophages may have anti-tumoral properties but tend to become anti-inflammatory and pro-tumorigenic in the TME. Most literature discusses macrophages as one of two phenotypes – the classically activated, pro-inflammatory M1 macrophage or the alternatively activated, anti-inflammatory, pro-tumor M2 macrophage. While this dichotomization oversimplifies the complex and dynamic behavior of macrophages, especially for M2 macrophages where it is now recognized that there are numerous functionally and characteristically distinct subtypes [84], these classifications remain useful for characterizing their roles in cancer. Tumor-associated macrophages (TAMs) that resemble the M2 phenotype can stimulate angiogenesis, enhance tumor cell invasion and extravasation, and suppress T cell activation and effector functions toward malignant cells [85]. A large presence of M2-like TAMs have been shown to correlate with increased tumor sizes, higher proliferation, and reduced overall survival in numerous cancer types, including breast cancer [86], non-small cell lung cancer [87], and prostate cancer [88]. Understanding the metabolic configurations of anti-inflammatory TAMs and how they differ from pro-inflammatory TAMs could help drive therapeutic approaches that can reprogram TAM phenotypes to switch a “cold,” immunosuppressive TME into one that can be challenged by the immune system.

As macrophages are polarized toward an M1 phenotype, they utilize aerobic glycolysis similar to the Warburg effect seen in cancer cells. The switch from oxidative phosphorylation to aerobic glycolysis occurs rapidly compared to mitochondrial biogenesis and allows glycolytic intermediates to be shuttled into the pentose phosphate pathway (PPP), where NADPH is generated for NADPH oxidase production of ROS [89,90]. On the opposite spectrum, polarization of TAMs to an M2 phenotype is generally accepted to be marked by an increase in FAO as they are exposed to cancer cell-secreted fatty acids within the TME [91,92]. However, recent literature suggests that simply blocking fatty acid uptake and oxidation to therapeutically induce an M2 to M1 switch in TAMs would greatly oversimplify the metabolic nature of TAM polarization. Which exact combination of saturated and unsaturated fatty acids are critical for M2 polarization and whether or not the full spectrum of hydrolyzed products from circulating lipoproteins instead of just FFAs are required have not yet been fully elucidated [93–96]. Regardless of the source, CD36 seems to be an active transporter for immunosuppressive TAMs, and studies show these cells have increased lipid accumulation and FAO, which is required for immune suppressive activity in both murine and human macrophages [97,98]. In contrast, some argue that FAO is indispensable for M2-like macrophages [99]. In other macrophage subsets, increased fatty acid uptake and oxidation, although correlating to an M2 phenotype, may be responsible for the secretion of pro-inflammatory cytokines from these cells such as CXCL10, IL-1β, and IL-10, which could have competing downstream effects by increasing the recruitment of effector T cells and natural killer (NK) cells or inducing tumor cell migration [100–102]. Further studies are required to determine how M2-like TAMs utilize fatty acids from the microenvironment and FAO before treatments targeting these pathways can be effective.

3.2. T cells

T cells play a critical role in immunity, including the response to cancer. CD8+ T cell infiltration into tumors has been associated with positive patient outcomes as tumor-specific antigen recognition allows CD8+ effector T cells (Teffs) to destroy cancer cells via perforin, granzymes, and other effector molecules. CD4+ T cells are complex and can be classified as anti-tumor and pro-inflammatory T-helper 1 (Th1) cells, immunosuppressive T-helper 2 (Th2) cells, the ambiguous T-helper 17 (Th17) cells, or the immune regulatory T cells (Tregs). T cell infiltration and function are crucial to mitigating tumor growth and progression, which may be exploited therapeutically.

CD8+ Teffs are generally characterized by the utilization of aerobic glycolysis to maintain effector function, but this can be challenged depending on nutrient availability within the TME. Increased concentration of FFAs from circulation or within the TME correlate with reduced CD8+ cytotoxic T lymphocyte activity [103,104]. However, other studies discuss an effector-promoting response of fatty acids. As tumors develop areas of nutrient deprivation from depletion of glucose in their rapid proliferation and growth [105], tumor-infiltrating lymphocytes (TILs) rely on oxidative phosphorylation (OXPHOS) to maintain energy levels and effector functions [106]. When oxygen supply is limited, hypoxia-inducible factor-1α (HIF-1α) expression enhances glycolysis [107]. A lack of both oxygen and glucose may further shift the metabolic profile of TILs to increased fatty acid uptake and catabolism to maintain effector function, where a balance between FAO and ketone body metabolism is dependent on the extent of oxygen deprivation [106]. Interestingly, hypoxia increases CD8+ T cell-mediated tumor rejection compared to normoxic conditions [108]. Other studies show an enhancement of effector function with FAO, but these results may not be fully attributable to FAO as glycolysis is also upregulated [109]. In contrast, obesity-driven leptin/STAT3 signaling in breast cancer promotes FAO and reduces glycolysis, inhibiting effector functions and facilitating tumor growth [110]. While there are conflicting results regarding the role of fatty acids and their catabolism, the conditions in which they facilitate or inhibit CD8+ T cell effector functions are dependent on context. Further studies must be performed to determine when fatty acids are detrimental to effector functions in order to utilize metabolic-based therapies for tumor eradication. This is especially relevant in tumors that develop in fat-replete environments such as breast, prostate, colorectal, and ovarian cancers.

Although Th2 cells are associated with an immunosuppressive, wound healing function, the CD4+ T cell subtype most associated with immunosuppression is the Treg, which dampens T cell activity. Tregs are CD4+ T cells that express FoxP3, a master regulator of Treg development and function which improves fatty acid uptake, OXPHOS, and FAO. FoxP3 enhances Treg resistance to lipotoxic environments, such as the TME, without sacrificing glycolysis to allow for expansion [111]. Tregs have been shown to infiltrate tumors and to reflect poorly on patient prognosis [112,113]. By suppressing cytotoxic activity, Tregs are commonly thought to play a role in immune evasion of tumor cells and to potentially support other pro-tumor cell types such as M2 macrophages [114–116]. Tregs that infiltrate the TME are not only highly suppressive but also possess enhanced glycolytic rates and lipid biosynthesis while still relying on FAO more than conventional Tregs [114]. Within hypoxic environments, Tregs utilize extracellular FFAs to support suppression of CD8+ T cells [116], giving them an advantage over TME-associated Teffs. While these findings may seem contradictory where lipid uptake versus synthesis is concerned, Howie *et al.* posit that Tregs adjust their metabolism generously based on the availability of nutrients [111].

Intratumoral Tregs could also be supported by CD36-mediated metabolic adaptation, enabling them to improve mitochondrial fitness and biogenesis, survive, and take advantage of the high lactate environment while acquiring the aforementioned superior suppressive functions [111,114,117]. Not only do Tregs upregulate CD36 in the presence of melanoma cancer cell conditioned media, but inhibition of CD36 is sufficient to reduce the number and suppressive function of intratumoral Tregs. Because peroxisome proliferator-activated receptor (PPAR) signaling contributes to metabolic modulation, PPARβ is indispensable in the CD36-mediated increase in intratumoral Treg suppressive activity [111,117]. Taken together, targeting T cell metabolism in the TME may lead to improvements in cancer immunotherapy.

The importance of considering lipids in T cell effector functions goes beyond understanding their metabolism. Recent studies further highlight the therapeutic potential of the LPC-ATX-LPA axis in T cells to prevent tumor immune evasion. Most investigations of the impact of LPA signaling focus on naïve T cell homing to secondary lymphoid organs, where ATX is secreted from either high endothelial venules or stromal cells. ATX acts on serum LPC, producing LPA that signals through LPAR2 and promotes T cell motility [118–121]. This suggests that LPA signaling may improve the immune response against tumors considering solid tumors across many different cancer types contain vessels, including high endothelial venules, that support lymphocyte infiltration [122]. However, other studies show T cell cytotoxicity is impaired when LPA signals through LPAR5 in T cells [123,124]. These studies provide a potential therapeutic avenue to target LPAR5 for preventing tumor immune evasion.

3.3. Dendritic cells

Dendritic cells (DCs) are vital in the adaptive immune response as they mediate antigen presentation to T cells. As such, understanding their dysfunction may elucidate the causes behind ineffective immune cell response in the TME. While immature DCs lean on mitochondrial biogenesis, the activation process after toll-like receptor (TLR) stimulation increases both glycolysis and fatty acid synthesis with long-term survival typically represented by increased glycolysis and decreased OXPHOS [125]. Increased lipid accumulation within LDs in tumor-associated DCs causes DC dysfunction by reducing antigen presentation and results in poor stimulation of T cell responses [126–130]. Targeting macrophage scavenging receptor (MSR1 or CD204) [126], acetyl-CoA carboxylase (ACC) [126], or X-box binding protein 1 (XBP1) [128] abrogates the increased accumulation of lipids by tumor-associated DCs, leading to improved survival in preclinical models [128]. As the complete mechanism regarding how lipids affect DCs is not fully understood, further study of lipid-DC interaction could yield treatments to reinvigorate DC antigen presentation function and potentially increase anti-tumor immune response.

3.4. Natural killer cells

NK cells are rapid first responders of the innate immune response. Their recruitment to the TME is facilitated by pro-inflammatory cytokines, where they can be activated to recruit other immune cells [131]. Upon activation, NK cells experience upregulated mTORC1 signaling, increasing glucose uptake and aerobic glycolysis to produce interferon-γ (IFNγ) and granzyme B for their effector functions [132]. Their activation coincides with an increase in ATP Citrate Lyase (ACLY) expression and citrate transport into the cytosol, which may be related to acetylation and epigenetic control [133]. Several studies demonstrate that exogenous lipids can disrupt this metabolic programming and negatively affect NK cell effector functions and their ability to respond to stimuli, especially in the context of obesity [134–136]. As NK cells take up these fatty acids and store them in LDs to prevent lipotoxicity, there is also an increase in expression of additional lipid transporters and enzymes involved in FAO, which could limit the mTORC1-mediated glycolytic increase needed for the production of granzyme B and IFNγ, resulting in deficient NK cell effector function [137]. These findings have significant implications for tumors progressing in the TME and adipocyte-rich microenvironments.

After surgery in models of melanoma, colorectal, and breast cancers, NK cell cytotoxic function can become impaired, leading to recurrence and metastasis [138–140]. Surgery-treated NK cells from colorectal cancer patients form two subpopulations, with one showing increased accumulation of lipids corresponding to higher expression of the CD36, CD68, and MSR1 lipid transporters. These NK cells show defective function and are unable to respond to cancer cells [139]. These studies suggest that lipid uptake by NK cells both in the TME during progression and following treatment warrant further study.

3.5. Neutrophils and myeloid derived suppressor cells

Neutrophils, considered the most abundant immune cell in the

body, can also be recruited to the TME where, like macrophages, they can play an immune-suppressive or anti-tumorigenic role. However, their presence tends to facilitate tumor progression, and it appears that their metabolic profiles are involved [141]. Neutrophils mainly utilize glycolysis, displaying very few mitochondria and relying minimally on OXPHOS [142,143]. When glucose supply is low such as in the TME, neutrophils can utilize FAO, supporting ROS production and increasing T cell suppression [144]. This suggests that a switch from glycolysis to FAO in neutrophils can facilitate tumorigenesis through immune suppression, and this is observed in the morphologically similar polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs).

PMN-MDSCs represent the majority of the MDSC population in humans and mice. They are so similar in morphology to their neutrophil counterparts that they can only be separated from neutrophils through gradient centrifugation or by exploiting their overexpression of lectin-type oxidized LDL receptor-1 [145–147]. PMN-MDSCs perform similar functions to monocytic MDSCs in terms of immune suppression but function mostly through antigen-specific suppression by ROS-dependent nitration of T cell receptors [148]. PMN-MDSCs from tumor-bearing mice from lymphoma, Lewis lung carcinoma, colon carcinoma, and pancreatic cancer have increased lipid accumulation with high expression of the fatty acid transporter FATP2. Knocking out FATP2 results in the loss of PMN-MDSCs to suppress CD8 + T cells, implicating fatty acid uptake from the TME in PMN-MDSC tumor suppression [149]. Similar observations in PMN-MDSCs through other fatty acid transporters and binding proteins like CD36 [150] and Lipocalin 2 [151] have recently been reported. FAO may support immune suppression in PMN-MDSCs through ROS-produced peroxynitrite generation leading to T cell suppression [152]. Further understanding the role of fatty acids in neutrophil differentiation to MDSCs within the TME and the mechanisms that allow these metabolites to promote MDSC immune suppression presents a novel avenue for potential therapeutic targets in the TME.

4. Metabolic factors influencing treatment success and recurrence

Cancer therapies typically employ a combination of chemotherapy (CT), radiation therapy (RT), and surgery in addition to targeted therapies, such as monoclonal antibodies, small molecule inhibitors, or immunotherapies. In general, CT and RT target rapidly dividing cells but still have significant normal tissue toxicities. RT can be used as either a palliative or curative treatment for cancer and is currently used in over 50% of all cancer patients, typically in fractionated daily doses [153,154]. When used in conjunction with surgical intervention, RT aims to exploit the poor DNA damage response mechanisms of tumor cells left behind at the primary tumor site. Radiation damage causes direct DNA lesions, double-stranded breaks, and the generation of ROS that can lead to additional DNA damage or cause significant oxidative stress. CT can be used neoadjuvantly to reduce the tumor size before surgery and kill any micrometastases, adjuvantly to kill remaining tumor cells after surgery, and after remission to prevent relapse. Generally, these drugs are non-specific and can impact various phases of the cell cycle. A large portion of these chemotherapeutic agents cause genotoxicity, requiring the tumor cell to perform similar repair mechanisms in order to survive the resulting DNA damage.

Increased FAO is being recognized as a hallmark of RT and CT resistant tumor cells. As discussed previously, CPT1A on the outer mitochondrial membrane is the rate-limiting enzyme for long-chain FAO. CPT2 on the inner mitochondrial membrane releases acyl-CoA from acylcarnitine to begin the β-oxidation process, allowing acetyl-CoA to be utilized in the tricarboxylic acid (TCA) cycle. Human epidermal growth factor receptor 2 (HER2)-expressing radioresistant breast cancer cells and radioresistant breast cancer stem cells are characterized by high expression of CPT1A and CPT2 and increased FAO, and patients with high CPT1A and CPT2 have a poor prognosis. Radioresistant cells respond to ionizing radiation by increasing FAO and ATP generation. This leads to increased phosphorylation of ERK1/2, decreasing apoptosis and promoting a more aggressive phenotype [155]. In nasopharyngeal carcinoma, radioresistant cells also demonstrate increased FAO after ionizing radiation exposure, where overexpression of CPT1A enhances cell survival through utilization of LD-derived fatty acids for increased FAO [156,157]. Since prostate cancer relies more heavily on lipid β-oxidation and fatty acid synthesis than aerobic glycolysis like other cancers, RT is significantly more effective when combined with inhibition of FASN [158]. Acute myeloid leukemia cells found in gonadal adipose tissue are exposed to adipokines and fatty acids, leading to increased CD36 expression, fatty acid uptake, and FAO, promoting chemoresistance [159]. It is clear why drugs like etomoxir that block CPT1 and FAO are being explored as RT and CT sensitizing agents [155,157,160]. These studies show how CT and RT resistant cells increase FAO in response to treatment to enhance survival and promote aggressive phenotypes after recurrence. One hypothesis for the mechanism behind this survival could be due to glutathione generation, which has been shown to increase stem cell radioresistance in breast cancer [161]. Increased β-oxidation can lead to TCA-based citrate production that can be transformed into lactate or α-ketoglutarate in the cytoplasm, replenishing NADPH [162,163] and ultimately promoting glutathione generation to scavenge ROS [160,164].

Ionizing radiation and some chemotherapeutic agents like antitumor antibiotics can generate ROS, which can result in DNA damage but can also disrupt the electron transport chain, cause lipid peroxidation, and inhibit proper protein folding in the endoplasmic reticulum (ER) [165]. Some ER stress is generally positive for cell survival, but prolonged ER stress can lead to the unfolded protein response (UPR). Ionizing radiation has been shown to directly cause ER stress in a wide variety of normal and malignant cell types [166–171]. Chemotherapeutics like taxanes and antimetabolites have been observed to induce ER stress in cancer cells, with successful alleviation of this stress resulting in survival and resistance to treatment [172,173]. Other studies suggest that lipid synthesis and LD formation are required to resolve ER stress, indicating a potential link between radiation damage, ER stress, and lipid metabolism. Several studies show that the UPR response can upregulate lipid synthesis to increase ER membrane length and generate increased LDs which can help target misfolded proteins to the ER-associated degradation pathway [174–177]. Lipid synthesis, LD formation, and ER stress resolution following RT and CT are undoubtedly linked. These studies demonstrate that targeting fatty acid synthesis and LD formation in cancer cells during RT or CT may prevent ER stress mitigation and induce apoptosis to enhance therapeutic efficacy.

The LPC-ATX-LPA lipid signaling axis has also been implicated in cancer cell survival following RT and CT, especially in breast cancer. The stromal cells of adipose tissue secrete high levels of ATX in response to RT as demonstrated following irradiation of rat abdominal adipose tissue and human breast and neck adipose tissue [178]. Studies of radiation damage in rat intestinal epithelial cells show that LPA signaling through LPAR2 enhances DNA damage repair [179]. Similarly, increased plasma ATX concentrations are observed after fractionated radiation of murine mammary fat pads *in vivo* [180]. This signaling axis may promote cancer cell survival following treatment as inhibiting ATX in combination with fractionated RT *in vivo* results in decreased Ki67-positive breast cancer cells and increased expression of apoptotic markers [181]. Additionally, the LPC-ATX-LPA signaling axis may improve survival of cancer cells following CT treatment [181–184]. The processes involved in regulating tumor cell survival during treatment are summarized in Fig. 3.

5. Lipids and their role in metastasis

The process of metastatic colonization is an arduous journey for a cancer cell. A tumor cell must detach from the primary tumor and intravasate into the circulation, a harsh environment that kills most circulating tumor cells (CTCs). Eventually, a CTC may extravasate from

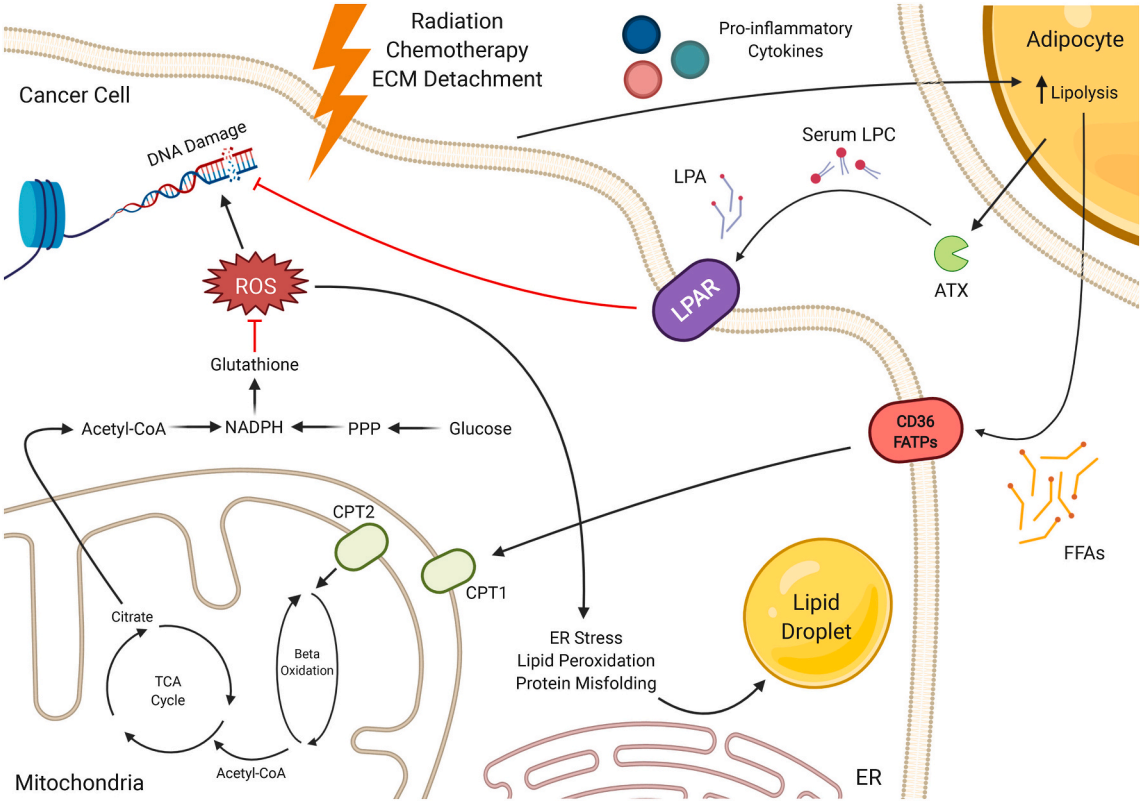

Fig. 3. The impact of lipid metabolism on treatment response and metastasis. Altered lipid metabolism profiles in tumor cells may provide survival advantages following therapy as well as in detached conditions promoting metastasis. RT, CT, and detachment can induce the formation of ROS, leading to DNA damage and ER stress [165–173]. Interestingly, LD formation has been correlated with UPR activation and ER stress reduction [174–177]. Cells that survive these stresses tend to have high expression of CPT1, the rate-limiting enzyme of FAO that transports long-chain fatty acids into the mitochondria, and high FAO rates [155–157,160,164,186,187]. This enables increased glutathione production through allowing high rates of aerobic glycolysis, facilitating the shuttling of glycolytic intermediates into the PPP [189], or the production of NADPH from cytosolic reactions of FAO-generated acetyl-CoA [162,163]. Adipocytes in the TME may influence these processes as pro-inflammatory cytokines secreted from damaged cells may induce lipolysis [26,29,30], resulting in a release of FFAs that can be taken up by fatty acid transporters. ATX secreted by treatment-damaged stromal cells [178] acts on serum LPC to produce LPA, which can signal through LPARs to improve DNA repair mechanisms and promote CT and RT cancer cell survival [181–184].

the circulation and find a supportive niche in a different tissue, where it may develop resistance to most treatments and stay quiescent until factors promote its growth into a metastatic lesion [185]. CTC cell death may be related to an inability to reduce ROS and decrease cellular stress as a result of detaching from the ECM. Some cancer cells overcome this ROS generation due to FAO-associated increased antioxidant generation [160,164,186,187]. This is further supported by evidence that the invasive front in lymph node metastases shows increased FAO and that lymph node metastases can be reduced through etomoxir treatment [188]. An advantage of increased FAO is that intermediates from glycolysis can be shuttled into the PPP to allow for control of intracellular ROS [189]. Cells that have high levels of *de novo* fatty acid synthesis and accumulation of lipids within LDs may have an adaptive advantage as they have the necessary fuel stored to allow for this increased oxidative metabolism [190–193]. However, a balance between too much and too little intracellular ROS may be required for a cell to metastasize, and FAO may be involved in the generation of ROS, resulting in increased markers associated with EMT and metastatic potential [194]. A reduction in fatty acid synthesis and fatty acid transport into mitochondria also shows a trend of decreasing metastasis through lower intracellular ROS levels. This mitigates DNA damage, which could normally give rise to mutations that enable cancer cell colonization of tissue sites different from their origin [195].

Tumor cells may be able to survive in the circulation through forming multicellular spheroids [196], where increased levels of unsaturated lipids may promote these micro-niches. The binding of secreted Angiotensin II to its receptor results in increased SCD1 expression, supporting the formation of cancer spheroids which are marked by increased ER stress response proteins [197]. Cell survival in these detached spheroids most likely requires successful resolution of ER stress, which may be facilitated through the increase in fluidity of the ER membrane as a result of increased unsaturated fatty acid anabolism [198,199]. Spheroid survival in colonized tissues may be improved by interactions with the stromal microenvironment. Lung fibroblasts secrete cathepsin B, which induces the upregulation of SCD1 in tumor cells through binding to Annexin A2 and induction of the PI3K/Akt/mTOR pathway. This increases metastatic nodules and results in decreased disease-free survival in patients with melanoma, clear cell renal cell carcinoma, pancreatic adenocarcinoma, and thymoma [200]. Targeting SCD1 in colon cancer decreases metastasis to the lungs [201], and this mechanism may be further implicated in breast cancer metastasis to the lungs [202]. In a contradictory view, these cell clusters that support metastasis may be characterized by hypoxia, in which case desaturation through SCD1 may be ineffective [196,203]. Instead of relying on *de novo* unsaturated fatty acid synthesis, cell clusters under hypoxia may require the uptake of these fatty acids from the environment. This could be an additional mechanism by which fatty acid transport proteins could be targeted to reduce metastasis [204,205].

These studies suggest that there may be significant heterogeneity in the ways cancer cells utilize lipids to survive in the circulation. The exact mechanisms could be related to the type of cancer, the specific microenvironment of the primary tumor, or whether the metastatic cascade occurs before or after primary treatment. Relying on FAO or lipid desaturation pathways may be related to whether or not the cells

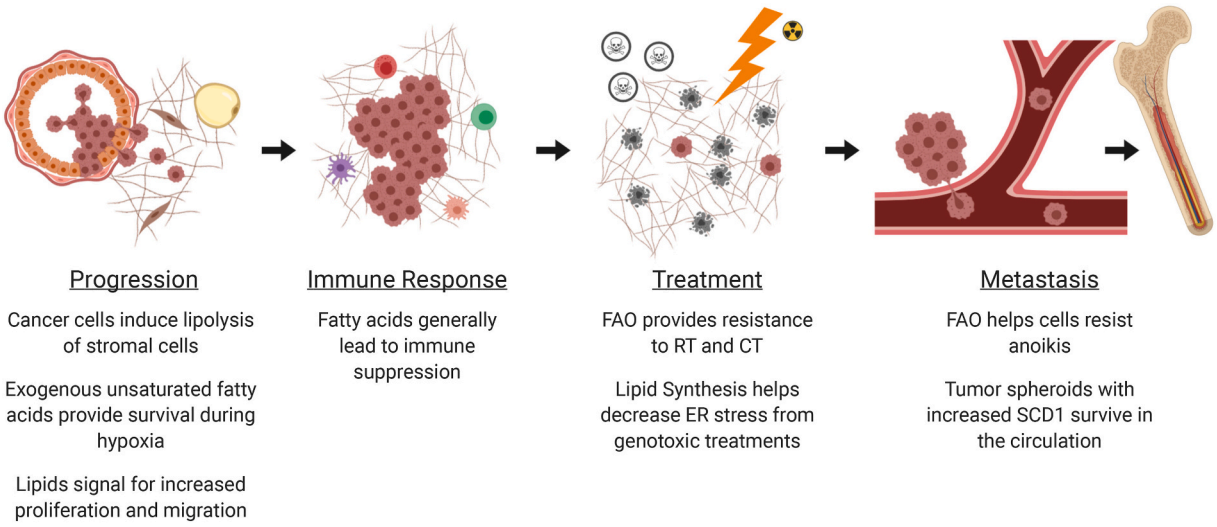

Fig. 4. Overarching themes of lipids in the tumor microenvironment. Lipids impact the TME at every stage of cancer progression. Lipids can be released from stromal cells as the tumor spreads into the surrounding microenvironment, providing fuel for new cell growth, inducing signaling to enhance migration, and suppressing the immune response. Utilizing lipids through FAO or lipid synthesis can promote survival for cancer cells experiencing cellular stress from RT, CT, or intravasation into the circulation. Targeting lipid metabolism reprogramming in cancer cells may lead to promising therapeutic strategies to ultimately improve patient outcomes.

form spheroids, experience hypoxia within the spheroid, or participate in single cell intravasation. Better understanding of the specific mechanisms initiating the metastatic cascade will help elucidate the therapeutic approach involving lipid metabolism that can be used to prevent cancer spread. An overview of these mechanisms is shown in Fig. 3.

6. Future perspectives for studying lipids and cancer

Recent literature demonstrates that there are numerous avenues through which targeting lipid metabolism and signaling within the TME may lead to improved treatments for primary cancerous lesions as well as treatment-resistant and metastatic cells (Fig. 4). Understanding how lipid metabolism impacts RT and CT resistance may lead to the design of drugs that target the lipid metabolic reprogramming of cancer cells to improve treatment efficacy. Many studies that analyze radioresistance use a single RT dose instead of a more clinically relevant fractionated regime. Exploring fractionated RT could alter how cancer cells utilize lipid metabolism to their survival advantage. Additionally, these studies typically evaluate single cell types and employ 2D cell culture before moving to *in vivo* studies. Including tumor-associated stromal cells may influence cancer cell survival following genotoxic treatments through secreted factors. Furthermore, developing 3D models may provide more physiologically relevant results.

Evaluating the metabolic impact and crosstalk between cancer cells and the adjacent normal tissue becomes even more important as drugs targeting fatty acid synthesis and oxidation are employed. We have shown that radiation damage to normal tissue can recruit CTCs and promote recurrence [206]. Determining how normal tissue cells incorporate lipid metabolism into their cell survival mechanisms can provide insights into the microenvironment of the residual tumor cells or recruited CTCs, which could further identify targets for recurrent disease. Ultimately, these drugs may need to be combined with tumor-targeting delivery mechanisms that minimize the potential off-target effects of systemic delivery.

As obesity rates continue to rise worldwide, studies on the increase in microenvironmental FFAs and adipokines will undoubtedly continue to be incorporated into research involving lipid metabolism and cancers that form within or near adipose tissue. Emerging studies have begun to evaluate metabolically-activated resident tissue macrophages that handle the high lipid load of dying hypertrophic adipocytes in obese adipose tissue, which are phenotypically distinct from either of the M1/M2 classifications [207]. These cells have already been linked to triple-negative breast cancer progression [208]. Understanding how these resident tissue immune cells impact lipid metabolic crosstalk between cancer cells and the stromal environment, especially in obesity, should be of focus for future studies. Further work in elucidating how obesity alters the immune response in cancer will also be vital going forward in order to determine how immune cells such as Tregs gain an advantage in the TME over Teffs and ultimately contribute to immune evasion. Understanding how lipid signaling and obesity, characterized by chronic inflammation, leads to poorer prognosis in cancers should be a key area of investigation.

It is clear that lipids within the TME can have a dramatic impact on cancer progression, treatment, recurrence, and metastasis. These ubiquitous biomolecules do not just play a role in the metabolism and signaling of cancer cells but are involved in the responses of tumor-recruited immune and stromal cells as well. Continuing to unravel the complex interactions between these various cell types and how lipids change their responses to one another will forge a path toward improved therapies and outcomes for cancer patients.

Declaration of Competing Interest

None declared.

Acknowledgements

This work was financially supported by the National Institutes of Health grant #R00CA201304 and the Ruth L. Kirschstein National Research Service Award grant #T32DK101003 (KCC). Figures were created with BioRender.com.

References

[1] O. Warburg, On the origin of cancer cells, Science (80-) 123 (1956) 309–314.
[2] M.G. Vander Heiden, L.C. Cantley, C.B. Thompson, Understanding the Warburg effect: the metabolic requirements of cell proliferation, Science (80-) 324 (2009) 1029–1033, https://doi.org/10.1126/science.1160809.
[3] N.N. Pavlova, C.B. Thompson, The emerging hallmarks of cancer metabolism, Cell Metab 23 (2016) 27–47, https://doi.org/10.1016/j.cmet.2015.12.006.
[4] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674, https://doi.org/10.1016/J.CELL.2011.02.013.
[5] K.E. Hopperton, R.E. Duncan, R.P. Bazinet, M.C. Archer, M.C. Archer, Fatty acid

synthase plays a role in cancer metabolism beyond providing fatty acids for phospholipid synthesis or sustaining elevations in glycolytic activity, Exp Cell Res 320 (2014) 302–310, https://doi.org/10.1016/j.yexcr.2013.10.016.
[6] C.-H. Yao, R. Fowle-Grider, N.G. Mahieu, G.-Y. Liu, Y.-J. Chen, R. Wang, et al., Exogenous fatty acids are the preferred source of membrane lipids in proliferating fibroblasts, Cell Chem Biol 23 (2016) 483–493, https://doi.org/10.1016/j.chembiol.2016.03.007.
[7] Wen Y-A, Xing X, Harris JW, Zaytseva YY, Mitov MI, Napier DL, et al. Adipocytes activate mitochondrial fatty acid oxidation and autophagy to promote tumor growth in colon cancer 2017. doi.https://doi.org/10.1038/cddis.2017.21.
[8] H. Lin, S. Patel, V.S. Affleck, I. Wilson, D.M. Turnbull, A.R. Joshi, et al., Fatty acid oxidation is required for the respiration and proliferation of malignant glioma cells, Neuro Oncol 19 (2017) 43–54, https://doi.org/10.1093/neuonc/now128.
[9] 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.
[10] 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 Discov 9 (2019) 617–627, https://doi.org/10.1158/2159-8290.CD-18-1212.
[11] M.G.K. Benesch, X. Tang, J. Dewald, W.-F. Dong, J.R. Mackey, D.G. Hemmings, et al., Tumor-induced inflammation in mammary adipose tissue stimulates a vicious cycle of autotaxin expression and breast cancer progression, FASEB J 29 (2015) 3990–4000, https://doi.org/10.1096/fj.15-274480.
[12] P.A. Volden, M.N. Skor, M.B. Johnson, P. Singh, F.N. Patel, M.K. Mcclintock, et al., Mammary adipose tissue-derived lysophospholipids promote estrogen receptor-negative mammary epithelial cell proliferation, Cancer Prev Res 9 (2016) 367–378, https://doi.org/10.1158/1940-6207.CAPR-15-0107.
[13] M. Blüher, Obesity: global epidemiology and pathogenesis, Nat Rev Endocrinol 15 (2019) 288–298, https://doi.org/10.1038/s41574-019-0176-8.
[14] M.D. Jensen, M.W. Haymond, R.A. Rizza, P.E. Cryer, J.M. Miles, Influence of body fat distribution on free fatty acid metabolism in obesity, J Clin Invest 83 (1989) 1168–1173, https://doi.org/10.1172/JCI113997.
[15] G. Boden, G.I. Shulman, Free fatty acids in obesity and type 2 diabetes: Defining their role in the development of insulin resistance and β-cell dysfunction, Eur J Clin Invest 32 (2002) 14–23, https://doi.org/10.1046/j.1365-2362.32.s3.3.x.
[16] M.R. Zanotelli, Z.E. Goldblatt, J.P. Miller, F. Bordeleau, J. Li, J.A. VanderBurgh, et al., Regulation of ATP utilization during metastatic cell migration by collagen architecture, Mol Biol Cell 29 (2018) 1–9, https://doi.org/10.1091/mbc.E17-01-0041.
[17] M. Zhang, J.S. Di Martino, R.L. Bowman, N.R. Campbell, S.C. Baksh, T. Simon-Vermot, et al., Adipocyte-derived lipids mediate melanoma progression via FATP proteins, Cancer Discov 8 (2018) 1006–1025, https://doi.org/10.1158/2159-8290.CD-17-1371.
[18] Y. Tan, K. Lin, Y. Zhao, Q. Wu, D. Chen, J. Wang, et al., Adipocytes fuel gastric cancer omental metastasis via PITPNC1-mediated fatty acid metabolic reprogramming, Theranostics 8 (2018) 5452–5468, https://doi.org/10.7150/thno.28219.
[19] F. Xiang, K. Wu, Y. Liu, L. Shi, D. Wang, G. Li, et al., Omental adipocytes enhance the invasiveness of gastric cancer cells by oleic acid-induced activation of the PI3K-Akt signaling pathway, Int J Biochem Cell Biol 84 (2017) 14–21, https://doi.org/10.1016/j.biocel.2016.12.002.
[20] 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.
[21] A. Ladanyi, A. Mukherjee, H.A. Kenny, A. Johnson, A.K. Mitra, S. Sundaresan, et al., Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis, Oncogene 37 (2018) 2285–2301, https://doi.org/10.1038/s41388-017-0093-z.
[22] D. Estève, M. Roumiguié, C. Manceau, D. Milhas, C. Muller, Periprostatic adipose tissue: A heavy player in prostate cancer progression, Curr Opin Endocr Metab Res 10 (2020) 29–35, https://doi.org/10.1016/j.coemr.2020.02.007.
[23] 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.
[24] 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), https://doi.org/10.1186/s40170-016-0163-7.
[25] 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), https://doi.org/10.1186/s12964-018-0221-6.
[26] Y.Y. Wang, C. Attané, 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.
[27] B. Dirat, L. Bochet, M. Dabek, D. Ele Daviaud, S. Ephanie Dauvillier, B. Majed, et al., Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion, Cancer Res 71 (2011) 2455–2465, https://doi.org/10.1158/0008-5472.CAN-10-3323.
[28] K. Fujisaki, H. Fujimoto, T. Sangai, T. Nagashima, M. Sakakibara, N. Shiina, et al., Cancer-mediated adipose reversion promotes cancer cell migration via IL-6 and MCP-1, Breast Cancer Res Treat 150 (2015) 255–263, https://doi.org/10.1007/s10549-015-3318-2.
[29] M. Petruzzelli, M. Schweiger, R. Schreiber, R. Campos-Olivas, M. Tsoli, J. Allen, et al., A switch from white to brown fat increases energy expenditure in cancer-associated cachexia, Cell Metab 20 (2014) 433–447, https://doi.org/10.1016/j.cmet.2014.06.011.
[30] S. Wueest, D. Konrad, The role of adipocyte-specific IL-6-type cytokine signaling in FFA and leptin release, Adipocyte 7 (2018) 226–228, https://doi.org/10.1080/21623945.2018.1493901.
[31] U. Rozovski, D.M. Harris, P. Li, Z. Liu, P. Jain, A. Ferrajoli, et al., STAT3-activated CD36 facilitates fatty acid uptake in chronic lymphocytic leukemia cells, Oncotarget 9 (2018) 21268–21280, https://doi.org/10.18632/oncotarget.25066.
[32] T. Su, C. Huang, C. Yang, T. Jiang, J. Su, M. Chen, et al., Apigenin inhibits STAT3/CD36 signaling axis and reduces visceral obesity, Pharmacol Res 152 (2020) 104586, , https://doi.org/10.1016/j.phrs.2019.104586.
[33] J.M. Wentworth, G. Naselli, W.A. Brown, L. Doyle, B. Phipson, G.K. Smyth, et al., Pro-inflammatory CD11c CD206 adipose tissue macrophages are associated with insulin resistance in human obesity, Diabetes 59 (2010) 1648–1656, https://doi.org/10.2337/db09-0287.
[34] S. Guaita-Esteruelas, A. Bosquet, P. Saavedra, J. Gumà, J. Girona, Lam EW-F, et al., Exogenous FABP4 increases breast cancer cell proliferation and activates the expression of fatty acid transport proteins, Mol Carcinog 56 (2017) 208–217, https://doi.org/10.1002/mc.22485.
[35] J. Hao, Y. Zhang, X. Yan, F. Yan, Y. Sun, J. Zeng, et al., Circulating adipose fatty acid binding protein is a new link underlying obesity-associated breast/mammary tumor development, Cell Metab 28 (2018) 689–705.e5, https://doi.org/10.1016/j.cmet.2018.07.006.
[36] F. Yan, N. Shen, J.X. Pang, Y.W. Zhang, E.Y. Rao, A.M. Bode, et al., Fatty acid-binding protein FABP4 mechanistically links obesity with aggressive AML by enhancing aberrant DNA methylation in AML cells, Leukemia 31 (2017) 1434–1442, https://doi.org/10.1038/leu.2016.349.
[37] M.S. Shafat, T. Oellerich, S. Mohr, S.D. Robinson, D.R. Edwards, C.R. Marlein, et al., Leukemic blasts program bone marrow adipocytes to generate a protumoral microenvironment, Blood 129 (2017) 1320–1332, https://doi.org/10.1182/blood-2016-08-734798.
[38] Z. Tang, Q. Shen, H. Xie, X. Zhou, J. Li, J. Feng, et al., Elevated expression of FABP3 and FABP4 cooperatively correlates with poor prognosis in non-small cell lung cancer (NSCLC), Oncotarget 7 (2016) 46253–46262, https://doi.org/10.18632/oncotarget.10086.
[39] K.M. Gharpure, S. Pradeep, M. Sans, R. Rupaimoole, C. Ivan, S.Y. Wu, et al., FABP4 as a key determinant of metastatic potential of ovarian cancer, Nat Commun 9 (2018) 1–14, https://doi.org/10.1038/s41467-018-04987-y.
[40] D. Lee, K. Wada, Y. Taniguchi, H. Al-Shareef, T. Masuda, Y. Usami, et al., Expression of fatty acid binding protein 4 is involved in the cell growth of oral squamous cell carcinoma, Oncol Rep 31 (2014) 1116–1120, https://doi.org/10.3892/or.2014.2975.
[41] W.J. Chen, C.C. Ho, Y.L. Chang, H.Y. Chen, C.A. Lin, T.Y. Ling, et al., Cancer-associated fibroblasts regulate the plasticity of lung cancer stemness via paracrine signalling, Nat Commun 5 (2014) 1–17, https://doi.org/10.1038/ncomms4472.
[42] Y. Yu, C.H. Xiao, L.D. Tan, Q.S. Wang, X.Q. Li, Y.M. Feng, Cancer-associated fibroblasts induce epithelial-mesenchymal transition of breast cancer cells through paracrine TGF-β signalling, Br J Cancer 110 (2014) 724–732, https://doi.org/10.1038/bjc.2013.768.
[43] L.J.A.C. Hawinkels, M. Paauwe, H.W. Verspaget, E. Wiercinska, J.M. Van Der Zon, K. Van Der Ploeg, et al., Interaction with colon cancer cells hyperactivates TGF-β signaling in cancer-associated fibroblasts, Oncogene 33 (2014) 97–107, https://doi.org/10.1038/onc.2012.536.
[44] T. Nagasaki, M. Hara, H. Nakanishi, H. Takahashi, M. Sato, H. Takeyama, Interleukin-6 released by colon cancer-associated fibroblasts is critical for tumour angiogenesis: Anti-interleukin-6 receptor antibody suppressed angiogenesis and inhibited tumour-stroma interaction, Br J Cancer 110 (2014) 469–478, https://doi.org/10.1038/bjc.2013.748.
[45] F. Lopes-Coelho, S. Andr, A.F. Elix, J. Serpa, Breast cancer metabolic cross-talk: Fibroblasts are hubs and breast cancer cells are gatherers of lipids, Mol Cell Endocrinol 462 (2017) 93–106, https://doi.org/10.1016/j.mce.2017.01.031.
[46] 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 - Mol Cell Res 1853 (2015) 3211–3223, https://doi.org/10.1016/j.bbamcr.2015.09.013.
[47] D. Černe, E. Melkič, Z. Trošt, M. Sok, J. Marc, Lipoprotein lipase activity and gene expression in lung aner and in adjacent noncancer lung tissue, Exp Lung Res 33 (2007) 217–225, https://doi.org/10.1080/01902140701481054.
[48] D. Cao, X. Song, L. Che, X. Li, M.G. Pilo, G. Vidili, et al., Both de novo synthetized and exogenous fatty acids support the growth of hepatocellular carcinoma cells, Liver Int 37 (2017) 80–89, https://doi.org/10.1111/liv.13183.
[49] W. Dong, H. Gong, G. Zhang, S. Vuletic, J. Albers, J. Zhang, et al., Lipoprotein lipase and phospholipid transfer protein overexpression in human glioma cells and their effect on cell growth, apoptosis, and migration, Acta Biochim Biophys Sin (Shanghai) 49 (2017) 62–73, https://doi.org/10.1093/ABBS/GMW117.
[50] N.B. Kuemmerle, E. Rysman, P.S. Lombardo, A.J. Flanagan, B.C. Lipe, W.A. Wells, et al., Lipoprotein lipase links dietary fat to solid tumor cell proliferation, Mol Cancer Ther 10 (2011) 427–436, https://doi.org/10.1158/1535-7163.MCT-10-0802.
[51] 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.

[52] A.M. Gouw, L.S. Eberlin, K. Margulis, D.K. Sullivan, G.G. Toal, L. Tong, et al., Oncogene KRAS activates fatty acid synthase, resulting in specific ERK and lipid signatures associated with lung adenocarcinoma, Proc Natl Acad Sci U S A 114 (2017) 4300–4305, https://doi.org/10.1073/pnas.1617709114.

[53] Y. Zhou, C. Niu, Y. Li, B. Gao, J. Zheng, X. Guo, et al., Fatty acid synthase expression and esophageal cancer, Mol Biol Rep 39 (2012) 9733–9739, https://doi.org/10.1007/s11033-012-1838-y.

[54] F.P. Kuhajda, K. Jenner, F.D. Wood, R.A. Hennigar, L.B. Jacobs, J.D. Dick, et al., Fatty acid synthesis: a potential selective target for antineoplastic therapy, Proc Natl Acad Sci U S A 91 (1994) 6379–6383, https://doi.org/10.1073/pnas.91.14.6379.

[55] R. Flavin, G. Zadra, M. Loda, Metabolic alterations and targeted therapies in prostate cancer, J Pathol 223 (2011) 284–295, https://doi.org/10.1002/path.2809.

[56] L. Weiss, G.E. Hoffmann, R. Schreiber, H. Andres, E. Fuchs, E. Korber, et al., Fatty-acid biosynthesis in man, a pathway of minor importance. purification, optimal assay conditions, and organ distribution of fatty-acid synthase, Biol Chem 367 (1986) 905–912, https://doi.org/10.1515/bchm3.1986.367.2.905.

[57] T. Kusakabe, M. Maeda, N. Hoshi, T. Sugino, K. Watanabe, T. Fukuda, et al., Fatty acid synthase is expressed mainly in adult hormone-sensitive cells or cells with high lipid metabolism and in proliferating fetal cells, J Histochem Cytochem 48 (2000) 613–622, https://doi.org/10.1177/002215540004800505.

[58] J.V. Swinnen, P.P. Van Veldhoven, L. Timmermans, E. De Schrijver, K. Brusselmans, F. Vanderhoydonc, et al., Fatty acid synthase drives the synthesis of phospholipids partitioning into detergent-resistant membrane microdomains, Biochem Biophys Res Commun 302 (2003) 898–903, https://doi.org/10.1016/S0006-291X(03)00265-1.

[59] 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.

[60] J. Li, S. Condello, J. Thomes-Pepin, T.D. Hurley, D. Matei, J.-X. Cheng, Lipid desaturation is a metabolic marker and therapeutic target of ovarian cancer stem cells, Cell Stem Cell 20 (2017) 303–314.e5, https://doi.org/10.1016/j.stem.2016.11.004.

[61] Y. Vivas-García, P. Falletta, J. Liebing, P. Louphrasitthiphol, Y. Feng, J. Chauhan, et al., Lineage-restricted regulation of SCD and fatty acid saturation by MITF controls melanoma phenotypic plasticity, Mol Cell 77 (2020) 120–137 e9 https://doi.org/10.1016/j.molcel.2019.10.014.

[62] J. Zhang, F. Song, X. Zhao, H. Jiang, X. Wu, B. Wang, et al., EGFR modulates monounsaturated fatty acid synthesis through phosphorylation of SCD1 in lung cancer, Mol Cancer 16 (2017), https://doi.org/10.1186/s12943-017-0704-x.

[63] J.J. Kamphorst, J.R. Cross, J. Fan, E. De Stanchina, R. Mathew, E.P. White, et al., Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids, Proc Natl Acad Sci U S A 110 (2013) 8882–8887, https://doi.org/10.1073/pnas.1307237110.

[64] D. Ackerman, S. Tumanov, B. Qiu, E. Michalopoulou, M. Spata, A. Azzam, et al., Triglycerides promote lipid homeostasis during hypoxic stress by balancing fatty acid saturation, Cell Rep 24 (2018) 2596–2605.e5, https://doi.org/10.1016/j.celrep.2018.08.015.

[65] Lingrand M, Lalonde S, Jutras-Carignan A, Bergeron KF, Rassart E, Mounier C. SCD1 activity promotes cell migration via a PLD-mTOR pathway in the MDA-MB-231 triple-negative breast cancer cell line. Breast Cancer 2020:1–13. doi.https://doi.org/10.1007/s12282-020-01053-8.

[66] K.E.N. Scott, F.B. Wheeler, A.L. Davis, M.J. Thomas, J.M. Ntambi, D.F. Seals, et al., Metabolic regulation of invadopodia and invasion by acetyl-CoA carboxylase 1 and De novo Lipogenesis, PLoS One 7 (2012) 1–14, https://doi.org/10.1371/journal.pone.0029761.

[67] I. Lazar, E. Clement, S. Dauvillier, D. Milhas, M. Ducoux-Petit, S. LeGonidec, et al., Adipocyte exosomes promote melanoma aggressiveness through fatty acid oxidation: a novel mechanism linking obesity and cancer, Cancer Res 76 (2016) 4051–4057, https://doi.org/10.1158/0008-5472.CAN-16-0651.

[68] Y. Tabe, S. Yamamoto, K. Saitoh, K. Sekihara, N. Monma, K. Ikeo, et al., Bone marrow adipocytes facilitate fatty acid oxidation activating AMPK and a transcriptional network supporting survival of acute monocytic leukemia cells, Cancer Res 77 (2017) 1453–1464, https://doi.org/10.1158/0008-5472.CAN-16-1645.

[69] L. Yang, X. Yu, Y. Yang, Autotaxin upregulated by STAT3 activation contributes to invasion in pancreatic neuroendocrine neoplasms, Endocr Connect 7 (2018) 1299–1307, https://doi.org/10.1530/EC-18-0356.

[70] J. Azare, A. Doane, K. Leslie, Q. Chang, M. Berishaj, J. Nnoli, et al., Stat3 mediates expression of autotaxin in breast cancer, PLoS One 6 (2011) e27851, , https://doi.org/10.1371/journal.pone.0027851.

[71] R. Schmid, K. Wolf, J.W. Robering, S. Strauß, P.L. Strissel, R. Strick, et al., ADSCs and adipocytes are the main producers in the autotaxin-lysophosphatidic acid axis of breast cancer and healthy mammary tissue in vitro, BMC Cancer 18 (2018) 1–11, https://doi.org/10.1186/s12885-018-5166-z.

[72] M.G.K. Benesch, X. Tang, T. Maeda, A. Ohhata, Y.Y. Zhao, B.P. C Kok, et al., Inhibition of autotaxin delays breast tumor growth and lung metastasis in mice, FASEB J 28 (2014) 2655–2666, https://doi.org/10.1096/fj.13-248641.

[73] D.B. Hoelzinger, M. Nakada, T. Demuth, T. Rosensteel, L.B. Reavie, M.E. Berens, Autotaxin: a secreted autocrine/paracrine factor that promotes glioma invasion, J Neurooncol 86 (2008) 297–309, https://doi.org/10.1007/s11060-007-9480-6.

[74] A. Xu, M. Ahsanul Kabir Khan, F. Chen, Z. Zhong, Chen H. chun, Y. Song, Overexpression of autotaxin is associated with human renal cell carcinoma and bladder carcinoma and their progression, Med Oncol 33 (2016) 1–8, https://doi.org/10.1007/s12032-016-0836-7.

[75] M.G.K. Benesch, Y.M. Ko, X. Tang, J. Dewald, A. Lopez-Campistrous, Y.Y. Zhao, et al., Autotaxin is an inflammatory mediator and therapeutic target in thyroid cancer, Endocr Relat Cancer 22 (2015) 593–607.

[76] C.C. Yun, Lysophosphatidic acid and autotaxin-associated effects on the initiation and progression of colorectal cancer, Cancers (Basel) 11 (2019) 958, https://doi.org/10.3390/cancers11070958.

[77] E.J. Seo, Y.W. Kwon, I.H. Jang, D.K. Kim, S.I. Lee, E.J. Choi, et al., Autotaxin regulates maintenance of ovarian cancer stem cells through lysophosphatidic acid-mediated autocrine mechanism, Stem Cells 34 (2016) 551–564, https://doi.org/10.1002/stem.2279.

[78] Y.C. Yung, N.C. Stoddard, J. Chun, LPA receptor signaling: pharmacology, physiology, and pathophysiology, J Lipid Res 55 (2014) 1192–1214, https://doi.org/10.1194/jlr.R046458.

[79] J. Park, J.-H. Jang, S. Oh, M. Kim, C. Shin, M. Jeong, et al., LPA-induced migration of ovarian cancer cells requires activation of ERM proteins via LPA1 and LPA2, Cell Signal 44 (2018) 138–147, https://doi.org/10.1016/j.cellsig.2018.01.007.

[80] S. Ishii, M. Hirane, K. Fukushima, A. Tomimatsu, N. Fukushima, T. Tsujiuchi, Diverse effects of LPA4, LPA5 and LPA6 on the activation of tumor progression in pancreatic cancer cells, Biochem Biophys Res Commun 461 (2015) 59–64, https://doi.org/10.1016/j.bbrc.2015.03.169.

[81] K. Takahashi, K. Fukushima, Y. Onishi, K. Inui, Y. Node, N. Fukushima, et al., Lysophosphatidic acid (LPA) signaling via LPA4 and LPA6 negatively regulates cell motile activities of colon cancer cells, Biochem Biophys Res Commun 483 (2016) 652–657, https://doi.org/10.1016/j.bbrc.2016.12.088.

[82] S.C. Lee, Y. Fujiwara, J. Liu, J. Yue, Y. Shimizu, D.D. Norman, et al., Autotaxin and LPA1 and LPA5 receptors exert disparate functions in tumor cells versus the host tissue microenvironment in melanoma invasion and metastasis, Mol Cancer Res 13 (2015) 174–185, https://doi.org/10.1158/1541-7786.MCR-14-0263.

[83] G. Solinas, G. Germano, A. Mantovani, P. Allavena, Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation, J Leukoc Biol 86 (2009) 1065–1073, https://doi.org/10.1189/jlb.0609385.

[84] F.O. Martinez, A. Sica, A. Mantovani, M. Locati, Macrophage activation and polarization, Front Biosci 13 (2008) 453–461, https://doi.org/10.2741/2692.

[85] R. Noy, J.W. Pollard, Tumor-associated macrophages: from mechanisms to therapy, Immunity 41 (2014) 49–61, https://doi.org/10.1016/j.immuni.2014.06.010.

[86] C. Medrek, F. Pontén, K. Jirström, K. Leandersson, The presence of tumor associated macrophages in tumor stroma as a prognostic marker for breast cancer patients, BMC Cancer 12 (2012) 1–9, https://doi.org/10.1186/1471-2407-12-306.

[87] A. Yuan, Y.J. Hsiao, H.Y. Chen, H.W. Chen, C.C. Ho, Y.Y. Chen, et al., Opposite effects of M1 and M2 macrophage subtypes on lung cancer progression, Sci Rep 5 (2015) 1–12, https://doi.org/10.1038/srep14273.

[88] A. Erlandsson, J. Carlsson, M. Lundholm, A. Fält, S.-O. Andersson, O. Andrén, et al., M2 macrophages and regulatory T cells in lethal prostate cancer, Prostate 79 (2019) 363–369, https://doi.org/10.1002/pros.23742.

[89] S. Galván-Peña, L.A.J. O'Neill, Metabolic reprograming in macrophage polarization, Front Immunol 5 (2014) 420, https://doi.org/10.3389/fimmu.2014.00420.

[90] A.J. Freemerman, A.R. Johnson, G.N. Sacks, J.J. Milner, E.L. Kirk, M.A. Troester, et al., Metabolic reprogramming of macrophages: glucose transporter 1 (GLUT1)-mediated glucose metabolism drives a proinflammatory phenotype, J Biol Chem 289 (2014) 7884–7896, https://doi.org/10.1074/jbc.M113.522037.

[91] F. Wang, S. Zhang, I. Vuckovic, C.D. Folmes, P.P. Dzeja, J. Herrmann, Glycolytic stimulation is not a requirement for M2 macrophage differentiation, Cell Metab 28 (2018) 463–475, https://doi.org/10.1016/j.cmet.2018.08.012.

[92] J. Cook, T. Hagemann, Tumour-associated macrophages and cancer, Curr Opin Pharmacol 13 (2013) 595–601, https://doi.org/10.1016/j.coph.2013.05.017.

[93] F. Xiu, L. Diao, P. Qi, M. Catapano, M.G. Jeschke, Palmitate differentially regulates the polarization of differentiating and differentiated macrophages, Immunology 147 (2016) 82–96, https://doi.org/10.1111/imm.12543.

[94] T. Schumann, T. Adhikary, A. Wortmann, F. Finkernagel, S. Lieber, E. Schnitzer, et al., Deregulation of PPARβ/δ target genes in tumor-associated macrophages by fatty acid ligands in the ovarian cancer microenvironment, Oncotarget 6 (2015) 13416–13433, https://doi.org/10.18632/oncotarget.3826.

[95] H. Podgornik, M. Sok, I. Kern, J. Marc, D. Cerne, Lipoprotein lipase in non-small cell lung cancer tissue is highly expressed in a subpopulation of tumor-associated macrophages, Pathol Pract 209 (2013) 516–520, https://doi.org/10.1016/j.prp.2013.06.004.

[96] N. Thyagarajan, J.D. Marshall, A.T. Pickett, C. Schumacher, Y. Yang, S.L. Christian, et al., Transcriptomic analysis of THP-1 macrophages exposed to lipoprotein hydrolysis products generated by lipoprotein lipase, Lipids 52 (2017) 189–205, https://doi.org/10.1007/s11745-017-4238-1.

[97] H. Wu, Y. Han, Y. Rodriguez Sillke, H. Deng, S. Siddiqui, C. Treese, et al., Lipid droplet-dependent fatty acid metabolism controls the immune suppressive phenotype of tumor-associated macrophages, EMBO Mol Med 11 (2019), https://doi.org/10.15252/emmm.201910698.

[98] P. Su, Q. Wang, E. Bi, X. Ma, L. Liu, M. Yang, et al., Enhanced lipid accumulation and metabolism are required for the differentiation and activation of tumor-associated macrophages, Cancer Res 80 (2020) 1438–1450, https://doi.org/10.1158/0008-5472.CAN-19-2994.

[99] D. Namgaladze, B. Brüne, Fatty acid oxidation is dispensable for human macrophage IL-4-induced polarization, Biochim Biophys Acta - Mol Cell Biol Lipids 1841 (2014) 1329–1335, https://doi.org/10.1016/j.bbalip.2014.06.007.

[100] Y. Zhang, Y. Sun, E. Rao, F. Yan, Q. Li, Y. Zhang, et al., Fatty acid-binding protein E-FABP restricts tumor growth by promoting ifn-b responses in tumor-associated macrophages, Cancer Res 74 (2014) 2986–2998, https://doi.org/10.1158/0008-5472.CAN-13-2689.

[101] Q. Zhang, H. Wang, C. Mao, M. Sun, G. Dominah, L. Chen, et al., Fatty acid

oxidation contributes to IL-1β secretion in M2 macrophages and promotes macrophage-mediated tumor cell migration, Mol Immunol 94 (2018) 27–35, https://doi.org/10.1016/j.molimm.2017.12.011.
[102] S. Chiba, T. Hisamatsu, H. Suzuki, K. Mori, M.T. Kitazume, K. Shimamura, et al., Glycolysis regulates LPS-induced cytokine production in M2 polarized human macrophages, Immunol Lett 183 (2017) 17–23, https://doi.org/10.1016/j.imlet.2017.01.012.
[103] R.E. Brown, R.W. Steele, D.J. Marmer, J.L. Hudson, M.A. Brewster, Fatty acids and the inhibition of mitogen-induced lymphocyte transformation by leukemic serum, J Immunol 131 (1983) 1011–1016.
[104] A.M. Kleinfeld, C. Okada, Free fatty acid release from human breast cancer tissue inhibits cytotoxic T-lymphocyte-mediated killing, J Lipid Res 46 (2005), https://doi.org/10.1194/jlr.M500151-JLR200.
[105] M.G.V. 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 (80-).
[106] Y. Zhang, R. Kurupati, L. Liu, X.Y. Zhou, G. Zhang, A. Hudaihed, et al., Enhancing CD8+ T cell fatty acid catabolism within a metabolically challenging tumor microenvironment increases the efficacy of melanoma immunotherapy, Cancer Cell 32 (2017) 377–391.e9, https://doi.org/10.1016/j.ccell.2017.08.004.
[107] Vaupel P, Kelleher DK, Hdckel M. Oxygenation status of malignant tumors: pathogenesis of hypoxia and significance for tumor therapy 2001. doi.https://doi.org/10.1053/sonc.2001.25398.
[108] Y. Gropper, T. Feferman, T. Shalit, T.-M. Salame, Z. Porat, G.S. Correspondence, Culturing CTLs under hypoxic conditions enhances their cytolysis and improves their anti-tumor function, Cell Rep 20 (2017) 2547–2555, https://doi.org/10.1016/j.celrep.2017.08.071.
[109] P.S. Chowdhury, K. Chamoto, A. Kumar, T. Honjo, PPAR-induced fatty acid oxidation in T cells increases the number of tumor-reactive CD8 + T cells and facilitates anti–PD-1 therapy, Cancer Immunol Res 6 (2018) 1375–1387, https://doi.org/10.1158/2326-6066.CIR-18-0095.
[110] C. Zhang, C. Yue, A. Herrmann, W. Huang, S. Priceman, H. Yu, STAT3 activation-induced fatty acid oxidation in CD8 + T effector cells is critical for obesity-promoted breast tumor growth, Cell Metab 31 (2020) 148–161, https://doi.org/10.1016/j.cmet.2019.10.013.
[111] D. Howie, S.P. Cobbold, E. Adams, A. Ten Bokum, A.S. Necula, W. Zhang, et al., Foxp3 drives oxidative phosphorylation and protection from lipotoxicity, JCI Insight 2 (2017) e89160, , https://doi.org/10.1172/jci.insight.89160.
[112] J. Shou, Z. Zhang, Y. Lai, Z. Chen, J. Huang, Worse outcome in breast cancer with higher tumor-infiltrating FOXP3+ Tregs: A systematic review and meta-analysis, BMC Cancer 16 (2016) 687, , https://doi.org/10.1186/s12885-016-2732-0.
[113] Y. Togashi, K. Shitara, H. Nishikawa, Regulatory T cells in cancer immunosuppression — implications for anticancer therapy, Nat Rev Clin Oncol 16 (2019) 356–371, https://doi.org/10.1038/s41571-019-0175-7.
[114] I. Pacella, C. Procaccini, C. Focaccetti, S. Miacci, E. Timperi, D. Faicchia, et al., Fatty acid metabolism complements glycolysis in th selective regulatory t cell expansion during tumor growth, Proc Natl Acad Sci U S A 115 (2018) E6546–E6555, https://doi.org/10.1073/pnas.1720113115.
[115] C. Liu, M. Chikina, R. Deshpande, A.V. Menk, T. Wang, T. Tabib, et al., Treg cells promote the SREBP1-dependent metabolic fitness of tumor-promoting macrophages via repression of CD8+ T cell-derived interferon-γ, Immunity 51 (2019) 381–397.e6, https://doi.org/10.1016/j.immuni.2019.06.017.
[116] J. Miska, C. Lee-Chang, A. Rashidi, M.E. Muroski, A.L. Chang, A. Lopez-Rosas, et al., HIF-1α is a metabolic switch between glycolytic-driven migration and oxidative phosphorylation-driven immunosuppression of tregs in glioblastoma, Cell Rep 27 (2019) 226–237.e4, https://doi.org/10.1016/j.celrep.2019.03.029.
[117] H. Wang, F. Franco, Y.C. Tsui, X. Xie, M.P. Trefny, R. Zappasodi, et al., CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors, Nat Immunol 21 (2020) 298–308, https://doi.org/10.1038/s41590-019-0589-5.
[118] Y. Zhang, Y.-C.M. Chen, M.F. Krummel, S.D. Rosen, Autotaxin through lysophosphatidic acid stimulates polarization, motility, and transendothelial migration of naive T cells, J Immunol 189 (2012) 3914–3924, https://doi.org/10.4049/jimmunol.1201604.
[119] A. Takeda, D. Kobayashi, K. Aoi, N. Sasaki, Y. Sugiura, H. Igarashi, et al., Fibroblastic reticular cell-derived lysophosphatidic acid regulates confined intranodal T-cell motility, Elife 5 (2016), https://doi.org/10.7554/eLife.10561.
[120] Z. Bai, L. Cai, E. Umemoto, A. Takeda, K. Tohya, Y. Komai, et al., Constitutive lymphocyte transmigration across the basal lamina of high endothelial venules is regulated by the autotaxin/lysophosphatidic acid axis, J Immunol 190 (2013) 2036–2048, https://doi.org/10.4049/jimmunol.1202025.
[121] S.A. Knowlden, T. Capece, M. Popovic, T.J. Chapman, F. Rezaee, M. Kim, et al., Regulation of T cell motility in vitro and in vivo by LPA and LPA2, PLoS One 9 (2014) e101655, , https://doi.org/10.1371/journal.pone.0101655.
[122] L. Martinet, I. Garrido, T. Filleron, Guellec S. Le, E. Bellard, J.J. Fournie, et al., Human solid tumors contain high endothelial venules: Association with T- and B-lymphocyte infiltration and favorable prognosis in breast cancer, Cancer Res 71 (2011) 5678–5687, https://doi.org/10.1158/0008-5472.CAN-11-0431.
[123] S.K. Oda, P. Strauch, Y. Fujiwara, A. Al-Shami, T. Oravecz, G. Tigyi, et al., Lysophosphatidic acid inhibits CD8 T cell activation and control of tumor progression, Cancer Immunol 1 (2013) 245–255, https://doi.org/10.1158/2326-6066.CIR-13-0043-T.
[124] D. Mathew, K.N. Kremer, P. Strauch, G. Tigyi, R. Pelanda, R.M. Torres, LPA5 is an inhibitory receptor that suppresses CD8 T-cell cytotoxic function via disruption of early TCR signaling, Front Immunol 10 (2019) 1159, https://doi.org/10.3389/fimmu.2019.01159.
[125] E.J. Pearce, B. Everts, Dendritic cell metabolism, Nat Publ Gr (2015), https://doi.org/10.1038/nri3771.
[126] D.L. Herber, W. Cao, Y. Nefedova, S.V. Novitskiy, S. Nagaraj, V.A. Tyurin, et al., Lipid accumulation and dendritic cell dysfunction in cancer, Nat Med 16 (2010) 880–886, https://doi.org/10.1038/nm.2172.
[127] W. Cao, R. Ramakrishnan, A. Vladimir, T. Filippo Veglia, T. Condamine, D.M. Andrew Amoscato, et al., Oxidized lipids block antigen cancer cross-presentation by dendritic cells in cancer (2014), https://doi.org/10.4049/jimmunol.1302801.
[128] J.R. Cubillos-Ruiz, P.C. Silberman, M.R. Rutkowski, S. Chopra, A. Perales-Puchalt, M. Song, et al., ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis, Cell 161 (2015) 1527–1538, https://doi.org/10.1016/j.cell.2015.05.025.
[129] F. Veglia, V.A. Tyurin, D. Mohammadyani, M. Blasi, E.K. Duperret, L. Donthireddy, et al., Lipid bodies containing oxidatively truncated lipids block antigen cross-presentation by dendritic cells in cancer, Nat Commun 8 (2017) 1–16, https://doi.org/10.1038/s41467-017-02186-9.
[130] F. Gao, C. Liu, J. Guo, W. Sun, L. Xian, D. Bai, et al., Radiation-driven lipid accumulation and dendritic cell dysfunction in cancer, Sci Rep 5 (2015) 9613, , https://doi.org/10.1038/srep09613.
[131] S. Paul, G. Lal, The molecular mechanism of natural killer cells function and its importance in cancer immunotherapy, Front Immunol 8 (2017) 1–15, https://doi.org/10.3389/fimmu.2017.01124.
[132] R.P. Donnelly, R.M. Loftus, S.E. Keating, K.T. Liou, C.A. Biron, C.M. Gardiner, et al., mTORC1-dependent metabolic reprogramming is a prerequisite for NK cell effector function, J Immunol 193 (2014) 4477–4484, https://doi.org/10.4049/jimmunol.1401558.
[133] N. Assmann, K.L. O'Brien, R.P. Donnelly, L. Dyck, V. Zaiatz-Bittencourt, R.M. Loftus, et al., Srebp-controlled glucose metabolism is essential for NK cell functional responses, Nat Immunol 18 (2017) 1197–1206, https://doi.org/10.1038/ni.3838.
[134] P. Yaqoob, E.A. Newsholme, P.C. Calder, Inhibition of natural killer cell activity by dietary lipids, Immunol Lett 41 (1994) 241–247, https://doi.org/10.1016/0165-2478(94)90140-6.
[135] L.M. Tobin, M. Mavinkurve, E. Carolan, D. Kinlen, E.C. O'Brien, M.A. Little, et al., NK cells in childhood obesity are activated, metabolically stressed, and functionally deficient, JCI Insight 2 (2017) e94939, , https://doi.org/10.1172/jci.insight.94939.
[136] S. Viel, L. Besson, E. Charrier, A. Marçais, E. Disse, J. Bienvenu, et al., Alteration of Natural Killer cell phenotype and function in obese individuals, Clin Immunol 177 (2017) 12–17, https://doi.org/10.1016/j.clim.2016.01.007.
[137] X. Michelet, L. Dyck, A. Hogan, R.M. Loftus, D. Duquette, K. Wei, et al., Metabolic reprogramming of natural killer cells in obesity limits antitumor responses, Nat Immunol 19 (2018) 1330–1340, https://doi.org/10.1038/s41590-018-0251-7.
[138] L.H. Tai, C.T. De Souza, S. Bélanger, L. Ly, A.A. Alkayyal, J. Zhang, et al., Preventing postoperative metastatic disease by inhibiting surgery-induced dysfunction in natural killer cells, Cancer Res 73 (2013) 97–107, https://doi.org/10.1158/0008-5472.CAN-12-1993.
[139] L.H. Tai, A.A. Alkayyal, A.L. Leslie, S. Sahi, S. Bennett, C. Tanese de Souza, et al., Phosphodiesterase-5 inhibition reduces postoperative metastatic disease by targeting surgery-induced myeloid derived suppressor cell-dependent inhibition of Natural Killer cell cytotoxicity, Oncoimmunology 7 (2018) e1431082, , https://doi.org/10.1080/2162402X.2018.1431082.
[140] R. Seth, L.-H. Tai, T. Falls, C.T. de Souza, J.C. Bell, M. Carrier, et al., Surgical stress promotes the development of cancer metastases by a coagulation-dependent mechanism involving natural killer cells in a murine model, Ann Surg 258 (2013) 158–168, https://doi.org/10.1097/SLA.0b013e31826fcbdb.
[141] S.B. Coffelt, M.D. Wellenstein, K.E. de Visser, Neutrophils in cancer: neutral no more, Nat Rev Cancer 16 (2016) 431–446, https://doi.org/10.1038/nrc.2016.52.
[142] N.A. Maianski, J. Geissler, S.M. Srinivasula, E.S. Alnemri, D. Roos, T.W. Kuijpers, Functional characterization of mitochondria in neutrophils: a role restricted to apoptosis, Cell Death Differ 11 (2004) 143–153, https://doi.org/10.1038/sj.cdd.4401320.
[143] N. Borregaard, T. Herlin, Energy metabolism of human neutrophils during phagocytosis, J Clin Invest 70 (1982) 550–557, https://doi.org/10.1172/JCI110647.
[144] C.M. Rice, L.C. Davies, J.J. Subleski, N. Maio, M. Gonzalez-Cotto, C. Andrews, et al., Tumour-elicited neutrophils engage mitochondrial metabolism to circumvent nutrient limitations and maintain immune suppression, Nat Commun 9 (2018) 1–13, https://doi.org/10.1038/s41467-018-07505-2.
[145] D.I. Gabrilovich, Myeloid-derived suppressor cells, Cancer Immunol Res 5 (2017) 3–8, https://doi.org/10.1158/2326-6066.CIR-16-0297.
[146] J. Zhou, Y. Nefedova, A. Lei, D. Gabrilovich, Neutrophils and PMN-MDSC: Their biological role and interaction with stromal cells, Semin Immunol 35 (2018) 19–28, https://doi.org/10.1016/j.smim.2017.12.004.
[147] T. Condamine, G.A. Dominguez, J.-I. Youn, A.V. Kossenkov, S. Mony, K. Alicea-Torres, et al., Lectin-type oxidized LDL receptor-1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients, Sci Immunol 1 (2016) aaf8943, https://doi.org/10.1126/sciimmunol.aaf8943.
[148] S. Nagaraj, K. Gupta, V. Pisarev, L. Kinarsky, S. Sherman, L. Kang, et al., Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer, Nat Med 13 (2007) 828–835, https://doi.org/10.1038/nm1609.
[149] F. Veglia, V.A. Tyurin, M. Blasi, A. De Leo, A.V. Kossenkov, L. Donthireddy, et al., Fatty acid transport protein 2 reprograms neutrophils in cancer, Nature 569 (2019) 73–78, https://doi.org/10.1038/s41586-019-1118-2.
[150] A.A. Al-Khami, L. Zheng, Valle L. Del, F. Hossain, D. Wyczechowska, J. Zabaleta, et al., Exogenous lipid uptake induces metabolic and functional reprogramming of

tumor-associated myeloid-derived suppressor cells, Oncoimmunology 6 (2017) e1344804, , https://doi.org/10.1080/2162402X.2017.1344804.
[151] T. Huang, Y. Li, Y. Zhou, B. Lu, Y. Zhang, D. Tang, et al., Stroke exacerbates cancer progression by upregulating LCN2 in PMN-MDSC, Front Immunol 11 (2020), https://doi.org/10.3389/fimmu.2020.00299.
[152] 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.
[153] B.D. Smith, J.R. Bellon, R. Blitzblau, G. Freedman, B. Haffty, C. Hahn, et al., Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline, Pract Radiat Oncol 8 (2018) 145–152, https://doi.org/10.1016/j.prro.2018.01.012.
[154] C. Allen, S. Her, D.A. Jaffray, Radiotherapy for cancer: present and future, Adv Drug Deliv Rev 109 (2017) 1–2, https://doi.org/10.1016/j.addr.2017.01.004.
[155] S. Han, R. Wei, X. Zhang, N. Jiang, M. Fan, J.H. Huang, et al., CPT1A/2-mediated FAO enhancement—a metabolic target in radioresistant breast cancer, Front Oncol 9 (2019), https://doi.org/10.3389/fonc.2019.01201.
[156] Q. Du, Z. Tan, F. Shi, M. Tang, L. Xie, L. Zhao, et al., PGC1α/CEBPB/CPT1A axis promotes radiation resistance of nasopharyngeal carcinoma through activating fatty acid oxidation, Cancer Sci 110 (2019) 2050–2062, https://doi.org/10.1111/cas.14011.
[157] Z. Tan, L. Xiao, M. Tang, J. Li, L. Li, F. Shi, et al., Targeting CPT1A-mediated fatty acid oxidation sensitizes nasopharyngeal carcinoma to radiation therapy, Theranostics 8 (2018) 2329–2347, https://doi.org/10.7150/thno.21451.
[158] H.-Y. Chuang, Y.-P. Lee, W.-C. Lin, Y.-H. Lin, J.-J. Hwang, Fatty acid inhibition sensitizes androgen-dependent and -independent prostate cancer to radiotherapy via FASN/NF-κB pathway, Sci Rep 9 (2019), https://doi.org/10.1038/s41598-019-49486-2.
[159] T. Farge, E. Saland, F. de Toni, N. Aroua, M. Hosseini, R. Perry, et al., Chemotherapy-resistant human acute myeloid leukemia cells are not enriched for leukemic stem cells but require oxidative metabolism, Cancer Discov 7 (2017) 716–735, https://doi.org/10.1158/2159-8290.CD-16-0441.
[160] Wang Y. nan, Zeng Z. lei, J. Lu, Y. Wang, Liu Z. xian, He M. ming, et al., CPT1A-mediated fatty acid oxidation promotes colorectal cancer cell metastasis by inhibiting anoikis, Oncogene 37 (2018) 6025–6040, https://doi.org/10.1038/s41388-018-0384-z.
[161] S.N. Rodman, J.M. Spence, T.J. Ronnfeldt, Y. Zhu, S.R. Solst, R.A. O'Neill, et al., Enhancement of radiation response in breast cancer stem cells by inhibition of thioredoxin- and glutathione-dependent metabolism, Radiat Res 186 (2016) 385–395, https://doi.org/10.1667/rr14463.1.
[162] A. Carracedo, L.C. Cantley, P.P. Pandolfi, Cancer metabolism: fatty acid oxidation in the limelight, Nat Rev Cancer 13 (2013) 227–232, https://doi.org/10.1038/nrc3483.
[163] X. Luo, C. Cheng, Z. Tan, N. Li, M. Tang, L. Yang, et al., Emerging roles of lipid metabolism in cancer metastasis, Mol Cancer 16 (2017) 1–16, https://doi.org/10.1186/s12943-017-0646-3.
[164] Z.T. Schafer, A.R. Grassian, L. Song, Z. Jiang, Z. Gerhart-Hines, H.Y. Irie, et al., Antioxidant and oncogene rescue of metabolic defects caused by loss of matrix attachment, Nature 461 (2009) 109–113, https://doi.org/10.1038/nature08268.
[165] W. Kim, S. Lee, D. Seo, D. Kim, K. Kim, E. Kim, et al., Cellular stress responses in radiotherapy, Cells 8 (2019) 1–18, https://doi.org/10.3390/cells8091105.
[166] B. Zhang, Y. Wang, X. Pang, Y. Su, G. Ai, T. Wang, ER stress induced by ionising radiation in IEC-6 cells, Int J Radiat Biol 86 (2010) 429–435, https://doi.org/10.3109/09553001003668014.
[167] B. Zhang, M. Wang, Y. Yang, Y. Wang, X. Pang, Y. Su, et al., ERp29 is a radiation-responsive gene in IEC-6 cell, J Radiat Res 49 (2008) 587–596, https://doi.org/10.1269/jrr.08014.
[168] E.S. Lee, H.-J. Lee, Y.-J. Lee, J.-H. Jeong, S. Kang, Y.-B. Lim, Chemical chaperones reduce ionizing radiation-induced endoplasmic reticulum stress and cell death in IEC-6 cells, Biochem Biophys Res Commun 450 (2014) 1005–1009, https://doi.org/10.1016/j.bbrc.2014.06.091.
[169] C.P. Hinzman, J.E. Baulch, K.Y. Mehta, K. Gill, C.L. Limoli, A.K. Cheema, Exposure to ionizing radiation causes endoplasmic reticulum stress in the mouse hippocampus, Radiat Res 190 (2018) 483–493, https://doi.org/10.1667/rr15061.1.
[170] Y. Akutsu, H. Matsubara, T. Urashima, A. Komatsu, H. Sakata, T. Nishimori, et al., Combination of direct intratumoral administration of dendritic cells and irradiation induces strong systemic antitumor effect mediated by GRP94/gp96 against squamous cell carcinoma in mice, Int J Oncol 31 (2007) 509–515, https://doi.org/10.3892/ijo.31.3.509.
[171] H. Kubota, T. Suzuki, J. Lu, S. Takahashi, K. Sugita, S. Sekiya, et al., Increased expression of GRP94 protein is associated with decreased sensitivity to X-rays in cervical cancer cell lines, Int J Radiat Biol 81 (2005) 701–709, https://doi.org/10.1080/09553000500434727.
[172] Y. Wu, M. Fabritius, C. Ip, Chemotherapeutic sensitization by endoplasmic reticulum stress: Increasing the efficacy of taxane against prostate cancer, Cancer Biol Ther 8 (2009) 146–152, https://doi.org/10.4161/cbt.8.2.7087.
[173] S. Tadros, S.K. Shukla, R.J. King, V. Gunda, E. Vernucci, J. Abrego, et al., de novo lipid synthesis facilitates gemcitabine resistance through endoplasmic reticulum stress in pancreatic cancer, Cancer Res 77 (2017) 5503–5517, https://doi.org/10.1158/0008-5472.CAN-16-3062.
[174] F. Romero, X. Hong, D. Shah, C.B. Kallen, I. Rosas, Z. Guo, et al., Lipid synthesis is required to resolve endoplasmic reticulum stress and limit fibrotic responses in the lung, Am J Respir Cell Mol Biol 59 (2018) 225–236, https://doi.org/10.1165/rcmb.2017-0340OC.
[175] J. Lee, T. Homma, T. Kurahashi, E.S. Kang, J. Fujii, Oxidative stress triggers lipid droplet accumulation in primary cultured hepatocytes by activating fatty acid synthesis, Biochem Biophys Res Commun 464 (2015) 229–235, https://doi.org/10.1016/j.bbrc.2015.06.121.
[176] J.S. Lee, R. Mendez, H.H. Heng, Z.Q. Yang, K. Zhang, Pharmacological ER stress promotes hepatic lipogenesis and lipid droplet formation, Am J Transl Res 4 (2012) 102–113.
[177] C. Piperi, C. Adamopoulos, A.G. Papavassiliou, XBP1: a pivotal transcriptional regulator of glucose and lipid metabolism, Trends Endocrinol Metab 27 (2016) 119–122, https://doi.org/10.1016/j.tem.2016.01.001.
[178] G. Meng, X. Tang, Z. Yang, M.G.K. Benesch, A. Marshall, D. Murray, et al., Implications for breast cancer treatment from increased autotaxin production in adipose tissue after radiotherapy, FASEB J 31 (2017) 4064–4077, https://doi.org/10.1096/fj.201700159R.
[179] A. Balogh, Y. Shimizu, S.C. Lee, D.D. Norman, R. Gangwar, M. Bavaria, et al., The autotaxin-LPA2 GPCR axis is modulated by γ-irradiation and facilitates DNA damage repair, Cell Signal 27 (2015) 1751–1762, https://doi.org/10.1016/j.cellsig.2015.05.015.
[180] G. Meng, M. Wuest, X. Tang, J. Dufour, Y. Zhao, J.M. Curtis, et al., Repeated fractions of X-radiation to the breast fat pads of mice augment activation of the autotaxin-lysophosphatidate-inflammatory cycle, Cancers (Basel) 11 (2019) 1816, https://doi.org/10.3390/cancers11111816.
[181] X. Tang, M. Wuest, M.G.K. Benesch, J. Dufour, Y.Y. Zhao, J.M. Curtis, et al., Inhibition of autotaxin with GLPG1690 increases the efficacy of radiotherapy and chemotherapy in a mouse model of breast cancer, Mol Cancer Ther 19 (2020) 63–74, https://doi.org/10.1158/1535-7163.MCT-19-0386.
[182] G. Schneider, Z.P. Sellers, A. Abdel-Latif, A.J. Morris, M.Z. Ratajczak, Bioactive lipids, LPC and LPA, are novel prometastatic factors and their tissue levels increase in response to radio/chemotherapy, Mol Cancer Res 12 (2014) 1560–1573, https://doi.org/10.1158/1541-7786.MCR-14-0188.
[183] N. Samadi, C. Gaetano, I.S. Goping, D.N. Brindley, Autotaxin protects MCF-7 breast cancer and MDA-MB-435 melanoma cells against taxol-induced apoptosis, Oncogene 28 (2009) 1028–1039, https://doi.org/10.1038/onc.2008.442.
[184] G. Venkatraman, M.G.K. Benesch, X. Tang, J. Dewald, T.P.W. McMullen, D.N. Brindley, Lysophosphatidate signaling stabilizes Nrf2 and increases the expression of genes involved in drug resistance and oxidative stress responses: implications for cancer treatment, FASEB J 29 (2015) 772–785, https://doi.org/10.1096/fj.14-262659.
[185] J. Massagué, A.C. Obenauf, Metastatic colonization by circulating tumour cells, Nature 529 (2016) 298–306, https://doi.org/10.1038/nature17038.
[186] B.T. Sawyer, L. Qamar, T.M. Yamamoto, A. McMellen, Z.L. Watson, J.K. Richer, et al., Targeting fatty acid oxidation to promote anoikis and inhibit ovarian cancer progression, Mol Cancer Res (2020), https://doi.org/10.1158/1541-7786.MCR-19-1057.
[187] A. van Weverwijk, N. Koundouros, M. Iravani, M. Ashenden, Q. Gao, G. Poulogiannis, et al., Metabolic adaptability in metastatic breast cancer by AKR1B10-dependent balancing of glycolysis and fatty acid oxidation, Nat Commun 10 (2019) 1–13, https://doi.org/10.1038/s41467-019-10592-4.
[188] C.-K. Lee, S.-H. Jeong, C. Jang, H. Bae, Y.H. Kim, I. Park, et al., Tumor metastasis to lymph nodes requires YAP-dependent metabolic adaptation Downloaded from, Science 363 (2019) 644–649, https://doi.org/10.1126/science.aav0173 (80-).
[189] L. Yang, Z. He, J. Yao, R. Tan, Y. Zhu, Z. Li, et al., Regulation of AMPK-related glycolipid metabolism imbalances redox homeostasis and inhibits anchorage independent growth in human breast cancer cells, Redox Biol 17 (2018) 180–191, https://doi.org/10.1016/j.redox.2018.04.016.
[190] H.J. Wright, J. Hou, B. Xu, M. Cortez, E.O. Potma, B.J. Tromberg, et al., CDCP1 drives triple-negative breast cancer metastasis through reduction of lipid-droplet abundance and stimulation of fatty acid oxidation, Proc Natl Acad Sci U S A 114 (2017) E6556–E6565, https://doi.org/10.1073/pnas.1703791114.
[191] R.R. Chen, M.M.H. Yung, Y. Xuan, S. Zhan, L.L. Leung, R.R. Liang, et al., Targeting of lipid metabolism with a metabolic inhibitor cocktail eradicates peritoneal metastases in ovarian cancer cells, Commun Biol 2 (2019) 1–15, https://doi.org/10.1038/s42003-019-0508-1.
[192] T. Sun, X. Zhong, H. Song, J. Liu, J. Li, F. Leung, et al., Anoikis resistant mediated by FASN promoted growth and metastasis of osteosarcoma, Cell Death Dis 10 (2019) 1–13, https://doi.org/10.1038/s41419-019-1532-2.
[193] J. Saab, M.L. Santos-Zabala, M. Loda, E.C. Stack, T.J. Hollmann, Fatty acid synthase and acetyl-CoA carboxylase are expressed in nodal metastatic melanoma but not in benign intracapsular nodal nevi, Am J Dermatopathol 40 (2018) 259–264, https://doi.org/10.1097/DAD.0000000000000939.
[194] C. Wang, L. Shao, C. Pan, J. Ye, Z. Ding, J. Wu, et al., Elevated level of mitochondrial reactive oxygen species via fatty acid β-oxidation in cancer stem cells promotes cancer metastasis by inducing epithelial-mesenchymal transition, Stem Cell Res Ther 10 (2019) 1–16, https://doi.org/10.1186/s13287-019-1265-2.
[195] K.M. Havas, V. Milchevskaya, K. Radic, A. Alladin, E. Kafkia, M. Garcia, et al., Metabolic shifts in residual breast cancer drive tumor recurrence, J Clin Invest 127 (2017) 2091–2105, https://doi.org/10.1172/JCI89914.
[196] V. Denes, M. Lakk, A. Makarovskiy, P. Jakso, S. Szappanos, L. Graf, et al., Metastasis blood test by flow cytometry: In vivo cancer spheroids and the role of hypoxia, Int J Cancer 136 (2015) 1528–1536, https://doi.org/10.1002/ijc.29155.
[197] Q. Zhang, S. Yu, M.M.T. Lam, T.C.W. Poon, L. Sun, Y. Jiao, et al., Angiotensin II promotes ovarian cancer spheroid formation and metastasis by upregulation of lipid desaturation and suppression of endoplasmic reticulum stress, J Exp Clin Cancer Res 38 (2019) 1–18, https://doi.org/10.1186/s13046-019-1127-x.
[198] A. Fujimoto, K. Kawana, A. Taguchi, K. Adachi, M. Sato, H. Nakamura, et al., Inhibition of endoplasmic reticulum (ER) stress sensors sensitizes cancer stem-like cells to ER stress-mediated apoptosis, Oncotarget 7 (2016) 51854–51864, https://

doi.org/10.18632/oncotarget.10126.
[199] D. Ackerman, M.C. Simon, Hypoxia, lipids, and cancer: surviving the harsh tumor microenvironment, Trends Cell Biol 24 (2014) 472–478, https://doi.org/10.1016/j.tcb.2014.06.001.
[200] G. Liu, S. Feng, L. Jia, C. Wang, Y. Fu, Y. Luo, Lung fibroblasts promote metastatic colonization through upregulation of stearoyl-CoA desaturase 1 in tumor cells, Oncogene 37 (2018) 1519–1533, https://doi.org/10.1038/s41388-017-0062-6.
[201] C. Liao, M. Li, X. Li, N. Li, X. Zhao, X. Wang, et al., Trichothecin inhibits invasion and metastasis of colon carcinoma associating with SCD-1-mediated metabolite alteration, Biochim Biophys Acta - Mol Cell Biol Lipids 1865 (2020) 158540, , https://doi.org/10.1016/j.bbalip.2019.158540.
[202] O. Vasiljeva, M. Korovin, M. Gajda, H. Brodoefel, L. Bojič, A. Krüger, et al., Reduced tumour cell proliferation and delayed development of high-grade mammary carcinomas in cathepsin B-deficient mice, Oncogene 27 (2008) 4191–4199, https://doi.org/10.1038/onc.2008.59.
[203] C.F. Labuschagne, E.C. Cheung, J. Blagih, M.-C. Domart, K.H. Vousden, Cell clustering promotes a metabolic switch that supports metastatic colonization, Cell Metab 30 (2019) 720–734.e5, https://doi.org/10.1016/j.cmet.2019.07.014.
[204] G. Pascual, A. Avgustinova, S. Mejetta, M. Martín, A. Castellanos, C.S.O. Attolini, et al., Targeting metastasis-initiating cells through the fatty acid receptor CD36, Nature 541 (2017) 41–45, https://doi.org/10.1038/nature20791.
[205] J. Pan, Z. Fan, Z. Wang, Q. Dai, Z. Xiang, F. Yuan, et al., CD36 mediates palmitate acid-induced metastasis of gastric cancer via AKT/GSK-3β/β-catenin pathway, J Exp Clin Cancer Res 35 (2019) 1–15, https://doi.org/10.1186/s13046-019-1049-7.
[206] M. Rafat, T.A. Aguilera, M. Vilalta, L.L. Bronsart, L.A. Soto, R. von Eyben, et al., Macrophages Promote Circulating Tumor Cell–Mediated Local Recurrence following Radiotherapy in Immunosuppressed Patients, Cancer Res 78 (2018) 4241–4252, https://doi.org/10.1158/0008-5472.CAN-17-3623.
[207] M. Kratz, B.R. Coats, K.B. Hisert, D. Hagman, V. Mutskov, E. Peris, et al., Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages, Cell Metab 20 (2014) 614–625, https://doi.org/10.1016/j.cmet.2014.08.010.
[208] P. Tiwari, A. Blank, C. Cui, K.Q. Schoenfelt, G. Zhou, Y. Xu, et al., Metabolically activated adipose tissue macrophages link obesity to triple-negative breast cancer, J Exp Med 216 (2019) 1345–1358, https://doi.org/10.1084/jem.20181616.