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Lipids in the Tumor Microenvironment: From Cancer Progression to Treatment

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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.

Keywords

Lipid Metabolism; Lipid Signaling; Tumor Microenvironment; Immune Response; Radiation Therapy; Metastasis

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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 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] [14,15].

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 also 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 roles 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; however, other cancers, including melanoma [17], gastric [18,19], ovarian [20,21], prostate [22], and colon cancers [7], are all influenced by interactions with surrounding adipose tissue. Many studies focus on the role of fatty acid translocase, also known as 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 also examined.

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 play a role in 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.

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]. However, 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, 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]. Additional literature demonstrates that breast cancer is highly influenced by the LPC-ATX-LPA axis. However, similar to pancreatic cancer, 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 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 play an anti-tumoral role but tend to adapt to one that is 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-1 β , 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 more complex in their role in cancer 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; however, 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-1 α (HIF-1 α) 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 also 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, PPAR β 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, however, 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 additional immune cells [131]. Upon activation, NK cells experience upregulated mTORC1 signaling, increasing glucose uptake and aerobic glycolysis to produce interferon- γ (IFN γ) 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 their 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 IFN γ , resulting in deficient NK 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]. However, 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 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]. However, 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, cells 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 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 the role of obesity in how cancer alters the immune response will also be vital going forward in order to determine how immune cells such as Tregs gain an advantage

in the TME over Tregs 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.

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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
L	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

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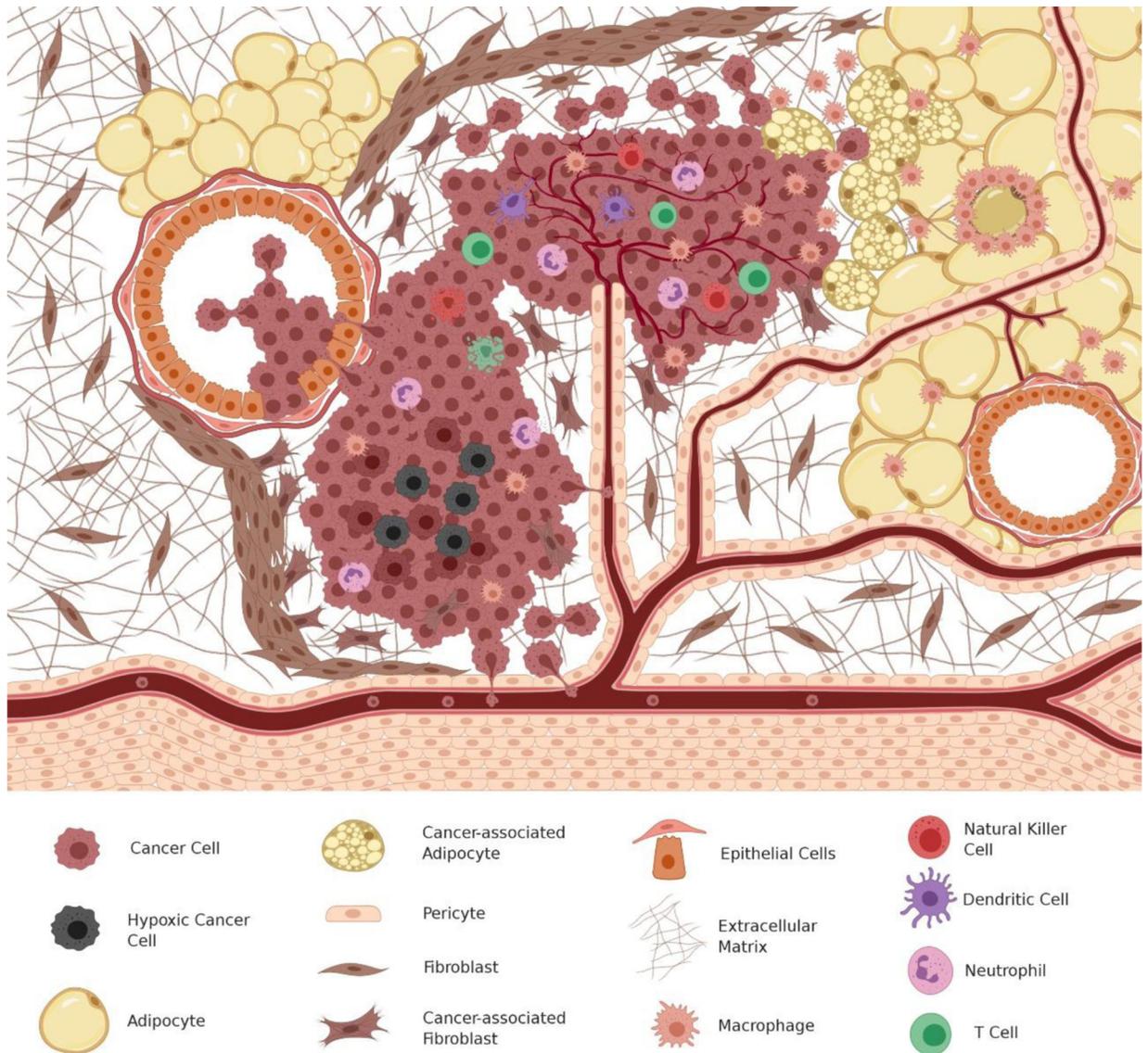


Fig. 1: Complex interactions within the tumor microenvironment (TME).

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.

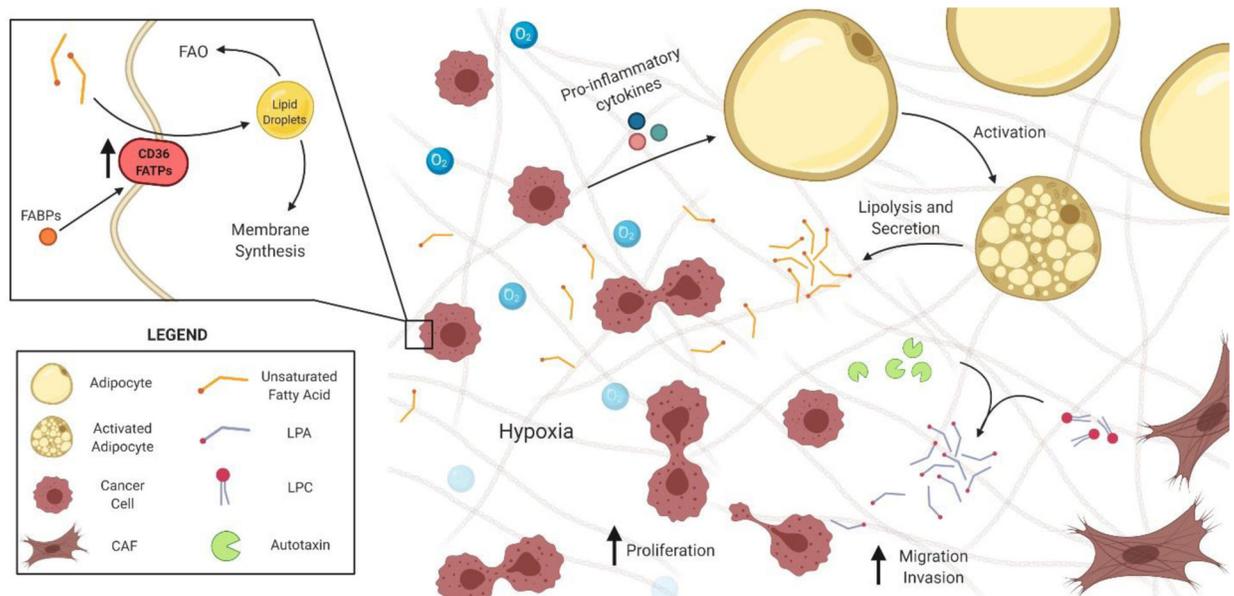


Fig. 2: Exogenous fatty acids from the TME promote cancer progression and survival.

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].

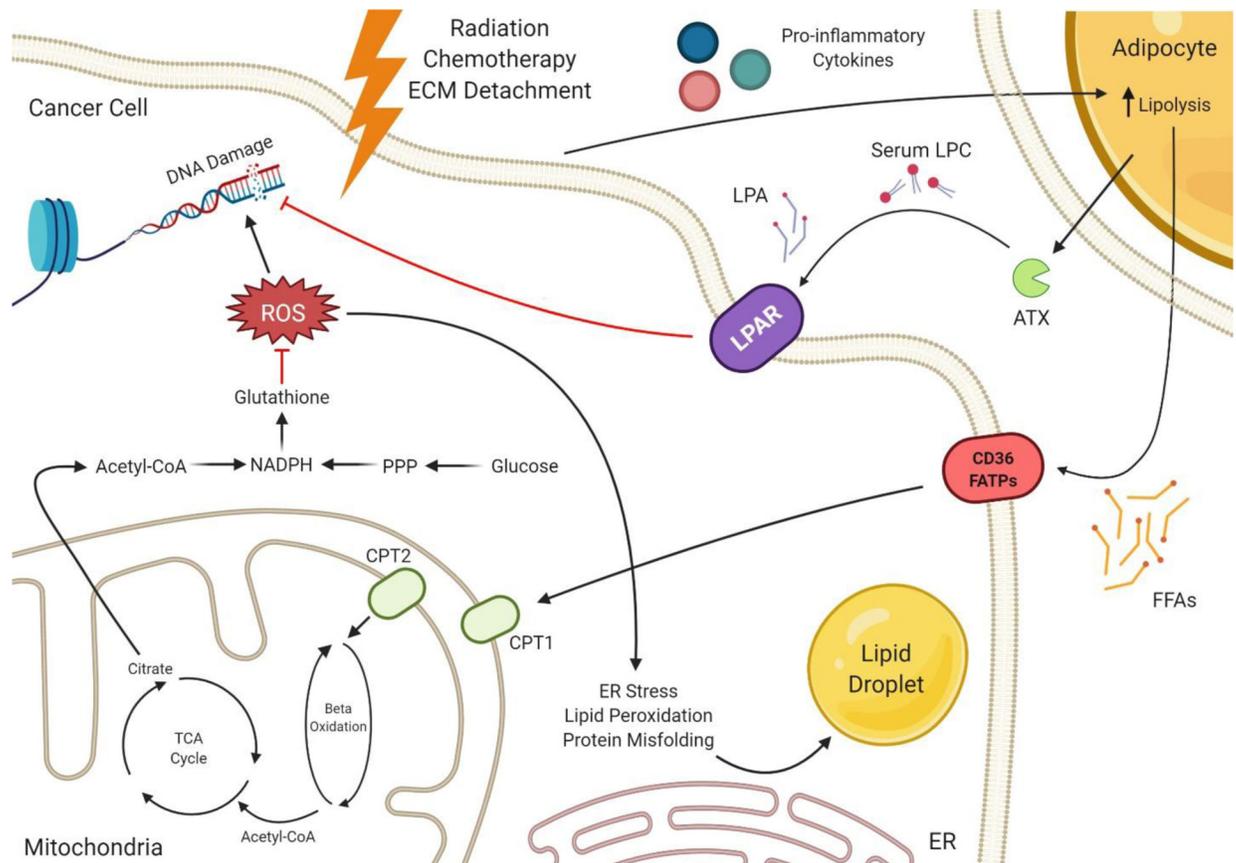


Fig. 3: The impact of lipid metabolism on treatment response and metastasis.

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].

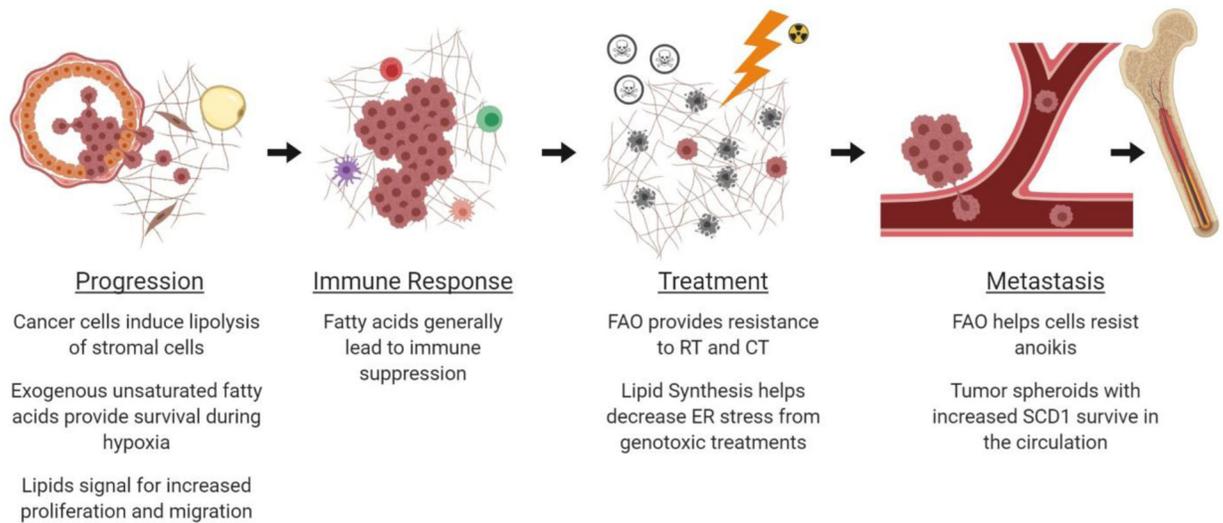


Fig. 4: Overarching themes of lipids in the tumor microenvironment.

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.

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]