Title: Lipid Metabolism in Cancer: New Perspectives and Emerging Mechanisms

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Abstract:

Tumors undergo metabolic transformations to sustain uncontrolled proliferation, avoid cell death and seed in secondary organs. An increased focus on cancer lipid metabolism has unveiled a number of mechanisms that promote tumor growth and survival, many of which are independent of classical cellular bioenergetics. These mechanisms include: modulation of ferroptotic-mediated cell death, support during tumor metastasis, and interactions with the cells of the tumor microenvironment. As such, targeting lipid metabolism for anti-cancer therapies is attractive, with recent work on small molecule inhibitors identifying compounds to target lipid metabolism. Here, we discuss these topics and identify open questions.

Introduction

Altered cellular metabolism and energetics is a well-established hallmark of cancer cells (Hanahan and Weinberg, 2011). Multiple pathways, mechanisms and proteins are involved in changing how cells utilize different metabolites and molecules to support aberrant cellular replication, dissemination from the primary tumor, secondary tumor establishment, and immune evasion. Lipid metabolism is often drastically altered in cells undergoing transformation to a malignant phenotype. Tumor cells can increase *de novo* lipogenesis, fatty acid (FA) uptake, FA oxidation (FAO) for energy production and lipid accumulation. The canonical rationale for elevated lipid metabolism in cancer cells is that increased lipids are required for plasma membrane synthesis and energy production. However, it is now well known that lipids play multiple other roles within cancer cells and the tumor microenvironment. For example, oncogenic signaling pathways (including the B-Raf kinase (BRAF) and epidermal growth factor receptor (EGFR)) drive dysregulated FA metabolism, influencing lipid membrane composition and saturation to modulate tolerance to reactive oxygen species (ROS) and cancer cell survival (Bi et al., 2019; Gimple et al., 2019; Talebi et al., 2018). Recent work finds that these changes enable invasion and metastasis, stimulate downstream signaling, regulate oxidative stress, and provide fuel for energy in various cellular stress situations (Ladanyi et al., 2018; Mullen et al., 2016; Pascual et al., 2017; Röhrig and Schulze, 2016; Slebe et al., 2016). While increased membrane lipid saturation can lead to endoplasmic reticulum (ER) stress and apoptosis (Ackerman and Simon, 2014), high amounts of polyunsaturated FA (PUFA) in membrane lipids sensitize to lipid peroxidation and ferroptosis, a recently identified form of non-apoptotic, iron- and PUFA-dependent cell death (Dixon et al., 2012; Doll et al., 2017; Friedmann Angeli et al., 2019a; Yang and Stockwell, 2016). Further, exposure to high-fat diets (HFD) can interact with cancer development and progression in a number of ways. For example, recent findings suggest that exposure to HFD can change normal liver metabolism similar to the metabolism found in hepatocellular carcinoma, and that this may prime liver tissue for carcinogenesis and tumor development (Broadfield et al., 2021). In this review, we discuss these mechanisms,

highlighting recent findings that are driving our understanding of non-canonical functions of lipids and their metabolism in the cancer cell.

The crosstalk between an altered lipid metabolism with the tumor microenvironment (TME) can strongly impact other cancer hallmarks, for example, through lipid mediators such as prostaglandin E_2 (PGE_2) and lysophosphatidic acid (LPA). These mechanisms can define tumor progression and resistance to different therapies by stimulating tumor promoting inflammation (Chiurchiù et al., 2018), enhancing angiogenesis (Hisano and Hla, 2019), influencing stromal cells and even allowing the escape from the immune system by drastically affecting the immune cell compartment (Baek et al., 2017; Zelenay et al., 2015). Here, we will discuss the interplay between the tumor and different components of the TME, including the altered lipid metabolism in tumor-associated immune cells.

Finally, after outlining how lipids support cancer development and progression, we discuss how these findings have identified therapeutic targets and opportunities for further development. We focus on the ongoing development of small-molecule inhibitors that are under pre-clinical and clinical investigation. The goal in targeting lipid metabolism in cancer cells is largely to enhance current treatment protocols, acting as adjuvant treatments. Here, we summarize current findings for these inhibitors, as well as how lipid metabolism can be targeted for immunometabolism.

Lipid metabolism: uptake, synthesis, catabolism, and storage

De novo lipogenesis is the process of lipid synthesis within a cell, and typically occurs in adipocytes and hepatocytes. (**Figure 1**). However, not all lipids can be synthesized *de novo*; alpha-linolenic acid (ALA) and linoleic acid (LA) are essential FA in humans and other mammals. These lipids must be consumed in the diet and taken up by cells for their use and downstream metabolism. Lipids in the local microenvironment can be brought across membranes via diffusion, FA transport proteins and FA translocase/CD36. Alternatively, low- and very low-density lipoproteins (LDL and VLDL, respectively) can provide lipids and to cancer cells (Guan et al., 2019; Lupien et al., 2020). For cellular lipogenesis, citrate is the starting point, where ATP-citrate lyase (ACLY) converts it to acetyl-CoA and oxaloacetate. Cytosolic citrate pools can be supported by the TCA cycle, or by glutamine metabolism via reductive carboxylation (**Figure 1**). Alternatively, acetate can bypass the requirement for citrate, directly contributing to cytosolic acetyl-CoA via acetyl-CoA synthetases, including acetyl-CoA synthetase 2 (ACSS2) (Pietrocola et al., 2015). Acetyl-CoA carboxylases 1 and 2 (ACACA and ACACB, respectively) then generate malonyl-CoA in the rate-limiting step of lipogenesis. FA synthase (FASN) then generates the lipid carbon chains by adding acetyl-CoA molecules, eventually producing palmitate (16:0).

Palmitate is a highly abundant saturated FA. It can be modified via stearoyl-CoA desaturase (SCD) and FA desaturase 2 (FADS2) to generate the mono-unsaturated FA (MUFA) palmitoleate and sapienate, respectively (Vriens et al., 2019). Elongation reactions can increase the carbon chain length by elongation of very long chain FA proteins (ELOVL enzymes). PUFA can be generated in cells from taken up essential FA (ALA and LA), however, the rate of conversion to well-known and bioactive PUFA species, such as eicosapentaenoic acid (EPA, 22:5n3) and docosahexaenoic acid (DHA, 22:6n3) are quite low (Burdge and Calder, 2005). Additional lipid classes, such as phospholipids, are generated by combining FA to a common backbone.

Phospholipids include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and phosphatidylinositol (PI), which are common building blocks for lipid bilayer membranes. Glycerol is another common backbone, and is used to generate diacylglycerols (DAG) and triacylglycerols (TAG). Glycerol-3-phosphate acyltransferase (GPAT) and acylglycerophosphate acyltransferase/lysophosphatidic acid acyltransferase (AGPAT/LPAAT) produce DAG species, with LPA and phosphatidic acid (PA) as intermediates (**Figure 1**). Diacylglycerol acyltransferases (DGAT) add an additional FA-CoA to DAG species to generate TAG species. TAG are the main storage form of lipids, and are sequestered in lipid droplets (LD), phospholipid enveloped vesicles that store and release lipids. Lipase enzymes, such as lipoprotein lipase (LPL) which hydrolyze TAG from lipoproteins to

release free-fatty acids (FFA). Degradation of intracellular TAG can be initiated by adipose triglyceride lipase (ATGL), hydrolyzing TAG to produce DAG, which can then further hydrolyzed by hormone sensitive lipase (HSL), producing monoacylglycerol (MAG) lipids. MAG lipase (MGL) hydrolyzes MAG to release the glycerol backbone, freeing the FA.

FA are classically described as an energy source through the process of FAO in the mitochondria. Carnitine palmitoyltransferase (CPT) 1 is the rate-limiting enzyme involved in mitochondrial FAO of long chain FA, mediating FA uptake into the mitochondria. Once inside the mitochondrial matrix, FA are available for oxidation by mitochondrial trifunctional protein (MTP), breaking down FA chains to produce acetyl-CoA for entry into the TCA cycle, and the cofactors NADH and $FADH_2$ for use in the electron transport chain to produce cellular ATP via oxidative phosphorylation. In this way, FAO produces energy for the cell.

Cholesterol is another type of lipid that can be synthesized and is critical for membrane structures. Acetyl-CoA is also the key metabolite for its production and is converted to acetoacetyl-CoA by acetyl-CoA acetyltransferase (ACAT). 3-hydroxy-3-methylglutaryl (HMG)-CoA is then synthesized through the condensation of acetyl-CoA with acetoacetyl-CoA by HMG-CoA synthetase (HMGCS). HMG-CoA reductase (HMGCR) is the rate limiting step in cholesterol synthesis, producing mevalonate (**Figure 1**). Mevalonate, like palmitate, is then available for further modifications to produce a variety of cholesterol species with biological uses and functions within the cell, such as membrane biogenesis.

Lipid metabolism reprogramming and dysregulation in cancer

To sustain growth and survival, tumors are very adaptable, allowing them to thrive even in the most adverse conditions. This plasticity is also manifested by different metabolic phenotypes that are shaped by genetic and epigenetic alterations, and these phenotypes are affected by the characteristics of the TME, such as nutrient and oxygen availability, pH levels, and interaction with other cells (Strickaert et al., 2017). Within these adaptations, lipid metabolism reprogramming plays a central role in promoting tumorigenesis and cancer progression (Beloribi-Djefaflia et al., 2016) and tumors can show pronounced alterations in their lipid signatures.

FA and cholesterol metabolism are dysregulated in cancer cells

The upregulation of FA synthesis is a classically described metabolic alteration in cancer. This provides phospholipids for cellular membranes to sustain proliferation, but also allows the synthesis of lipid mediators that play important roles in certain tumors (Röhrig and Schulze, 2016). This well documented phenomenon is achieved by the upregulation of various lipogenic enzymes. An example is ACLY, which has increased activity in human lung cancer (Migita et al., 2008), and is upregulated in human hepatocellular carcinoma (HCC) and in an *in vivo* murine liver cancer model (Calvisi et al., 2011). ACSS2 has also been reported to be dysregulated in cancer, supporting cytosolic acetyl-CoA levels which can then be used for FA synthesis. This enzyme correlated with poorer prognosis in cancer and is often highly expressed in glioblastoma, breast, ovarian and lung cancers (Schug et al., 2016). ACACA is increased in human and murine liver cancer (Calvisi et al., 2011; Nelson et al., 2017), as well as in human clear cell renal cell carcinoma (ccRCC) (Creighton et al., 2013). Moreover, FASN has been known for many years to be upregulated in several cancer types including breast (Kuhajda et al., 1994; Ricoult et al., 2016), prostate (Swinnen et al., 2002), liver (Calvisi et al., 2011), ccRCC (Creighton et al., 2013) and glioma (Tao et al., 2013). Furthermore, increased expression of FASN was associated with higher cancer grade in gliomas (Tao et al., 2013) and prostate cancer (Swinnen et al., 2002), and poorer prognosis in breast cancer (Kuhajda et al., 1994) and ccRCC (Creighton et al., 2013), highlighting the importance of FASN as a mediator of the lipogenic phenotype of transformed cells. Overall, increased expression or activity of lipogenic enzymes is a common feature among many caner types.

While lipids are required for elevated cell proliferation, certain lipid species can affect cellular stress and must be maintained in a certain balance. For example, the degree of FA unsaturation plays a key

role in this balance, and the saturation level of cell membrane lipids is a matter of life and death for the tumor cell (Ackerman and Simon, 2014; Friedmann Angeli et al., 2019b; Rysman et al., 2010). For instance, SCD drives the mono-unsaturation of FA species, and its overexpression has been found in various cancers to correlate with decreased survival (Peck and Schulze, 2016). Since the reaction catalyzed by SCD requires molecular oxygen, it can be hampered by hypoxic conditions, a consideration for the growth of solid tumors with disordered vascularization. In renal cancer and glioblastoma cell lines, serum and oxygen limitations decreased viability, an effect that was rescued by addition of the MUFA oleic acid (Young et al., 2013). Further, treatment with an SCD1 inhibitor phenocopied O_2 deprivation, and this state was also rescued by oleate, evidencing that unsaturated lipids are key nutrients for survival under hypoxia in these tumor cells (Young et al., 2013). Human breast, cervical and lung cancer cell lines were shown to compensate for hypoxic environments by scavenging unsaturated FA *in vitro* (Kamphorst et al., 2013). Furthermore, aside from increasing the expression of proteins regulating FA uptake, human glioblastoma cell lines can also upregulate SCD in response to hypoxia (Lewis et al., 2015). In a lipid-depleted microenvironment, SCD downregulation or inhibition can lead to a deficiency in unsaturated lipids, induce ER stress, and cell death, as shown in a human glioblastoma cell line (Griffiths et al., 2013). SREBP, a major regulator of cellular lipid metabolism, also plays a role in balancing lipid desaturation in cancer. A study employing human glioblastoma *in vitro* and *in vivo* showed that the loss of SREBP signaling impaired cell viability and growth through the uncoupling of FA synthesis from desaturation (Williams et al., 2013). While FA synthesis was maintained, desaturation capacity was lost due to a decrease in SCD1 activity, generating an imbalance between MUFA and saturated FA (SFA) causing lipotoxicity (Williams et al., 2013), a mechanism in which excessive FA accumulation in non-adipose cells generates cell dysfunction and death (Han and Kaufman, 2016). Furthermore, oleate supplementation restored growth in tumor cells and SCD1 knockdown phenocopied the effects of loss of SREBP activity, indicating the importance of this desaturation pathway in glioblastoma (Williams et al., 2013). In contrast, certain tumors are resistant to SCD inhibition, with the finding that various human cancer cell lines (liver, lung and prostate), some mouse HCCs and primary human liver and lung carcinomas can use FADS2 as an alternative desaturation pathway (Vriens et al., 2019). This enzyme, which is necessary to convert linoleic and α-linoleic acids into other PUFA including arachidonic acid (AA) (Zhang et al., 2016), generates unsaturated FA by converting palmitate (C16:0) into sapienate (*cis*-6-C16:1), supporting membrane synthesis and tumor cell proliferation (Vriens et al., 2019). In this study, human liver (HUH7) and lung cancer cell lines were resistant to *in vitro* SCD inhibition. Interestingly, concurrent SCD inhibition with *FADS2* silencing in these same cell lines led to inhibition of *in vitro* proliferation or cell death, while *in vivo* inhibition of these enzymatic activities employing HUH7 orthotopic liver xenografts led to a reduction in tumor growth (Vriens et al., 2019). Another study evidenced that mammalian target of rapamycin (mTOR) signaling and SREBP activity regulate FADS2-mediated sapienate production (Triki et al., 2020). Here, the inhibition of mTOR signaling or SREBP decreased FADS2 expression and sapienate synthesis in HUH7 cells *in vitro*, and mTOR inhibition exerted the same effects *in vivo* when these cells were injected as orthotopic liver xenografts. Furthermore, high expression of FADS2 was associated with decreased patient survival in bladder and renal cancer and mesothelioma (Triki et al., 2020). These studies highlight the flexibility of cancer cells to activate non-canonical lipid metabolism pathways to help maintain the balance between lipid saturation and unsaturation, therefore avoiding cellular stress and death.

Another common lipogenic pathway that is stimulated in cancer is the mevalonate pathway, leading to the production of cholesterol, a key molecule for cell membrane function, as well as other important molecules that can support tumor growth and progression (Mullen et al., 2016). For example, the cholesterol synthesis enzymes HMGCR, mevalonate kinase (MVK), and squalene synthase (SQS) were increased in human HCC and associated with poorer clinical outcome, and in an *in vivo* murine liver cancer model (Calvisi et al., 2011). Furthermore, overexpression of the catalytic domain of HMGCR was shown to increase transformation in human breast and liver tumor cells *in vitro* (Clendening et al., 2010). Injection of HMGCR-overexpressing liver cancer cells in immune-deficient mice led to increased tumor growth, and levels of mevalonate pathway genes correlated with poor prognosis in breast cancer patients (Clendening et al., 2010). These examples evidence the prominent role of this pathway in cancer cells' metabolic reprogramming.

Crosstalk between the TME and lipid metabolism in tumor cells

The TME is well known to affect cancer cell metabolism, providing nutrients, growth factors, and other extracellular molecules to tumor cells. Variable oxygen tension and hypoxia is one way in which the TME can impact cancer lipid metabolism. As mentioned above, tumor cells subjected to hypoxic environments can rely on FA uptake (Kamphorst et al., 2013; Young et al., 2013) and the expression of lipid uptake associated proteins (such as CD36 in lung, bladder, breast and ovarian cancer, and the LDL receptor (LDLR) in pancreatic cancer) are connected to worse patient prognosis (Guillaumond et al., 2015; Ladanyi et al., 2018; Pascual et al., 2017). Hypoxia-associated enhanced FA uptake can also lead to LD accumulation. For example, in human breast cancer and glioblastoma cell lines, hypoxia-inducible factor-1α (HIF-1α) induced expression of FA binding proteins 3 and 7 (FABP3/7), and adipophilin, which enabled increased FA uptake and LD formation, respectively (Bensaad et al., 2014). A recent study showed that breast cancer cells can take up VLDLs through a mechanism involving the VLDL receptor and LPL (which is highly expressed in certain tumor cells) (Lupien et al., 2020). Furthermore, they showed that the degree in which these breast cancer cells depend on lipid synthesis versus uptake varies according to VLDL availability and also among different breast cancer cell lines (Lupien et al., 2020). Other studies have also shown that LDLs can increase proliferation and migration of breast cancer cells and are associated with cancer progression, although the effects vary with different breast cancer types (Guan et al., 2019). These findings highlight the influence of lipid availability on cancer development, as it can affect the balance between lipid synthesis and uptake, with tumor cells adapting to their environment. Furthermore, adverse environmental conditions, such as high acidity (Corbet et al., 2016) or glucose deprivation (Wang et al., 2016b), can drive or promote the upregulation of FAO, and many tumors rely on this metabolic process for survival, such as in the case of certain lung (Padanad et al., 2016) and breast (Camarda et al., 2016) cancers. Tumor cells can upregulate enzymes involved in this pathway, such as CPT1 and CPT2 (Liu et al., 2016). Another example is acyl-CoA synthetase long chain (ACSL) family member 3, which turns FA into their corresponding acyl-CoA esters, and was shown to be upregulated and to promote FA uptake, lipid accumulation and FAO in lung cancer (Padanad et al., 2016), as well as to confer resistance to ferroptosis as discussed later in the review. In addition to modulating FA metabolism and uptake, the TME can also alter the mevalonate pathway in tumor cells. For example, an acidic extracellular environment increases cholesterol synthesis enzyme expression, supporting pancreatic cancer tumor growth; and this dysregulated gene expression was correlated to decreased survival in patients suffering from different cancers (Kondo et al., 2017).

Another important aspect of the TME are the other cell populations that interact with cancer cells. One example is that certain tumor cells can induce lipolysis in adjacent adipocytes (Argilés et al., 2014). The adipocyte-derived FA can be used and stored by cancer cells; and many tumor types, including colorectal (Wen et al., 2017), ovarian (Nieman et al., 2011) and breast (Wang et al., 2017) cancers, also upregulate FAO in order to harness this fuel. Adipocytes are abundant in the bone marrow, and have bidirectional interactions with tumor cells beyond the supply of lipids. For example, co-cultures of bone marrow adipocytes with melanoma cells were found to have decreased adiponectin, an anticancer adipokine, which was regulated in a tumor necrosis factor α (TNFα) manner (Morris et al., 2020). Furthermore, a recent publication showed that myeloma cells induce a senescent-like phenotype and abnormal metabolism in bone marrow adipocytes (Fairfield et al., 2021). In turn, the adipocytes can support myeloma cells resistance to dexamethasone treatments (Fairfield et al., 2021). In a murine model of prostate cancer, increased bone marrow adiposity via HFD feeding increased local prostate cancer cell growth, and caused a glycolytic shift in the tumor cells as compared to control diet (Diedrich et al., 2016). Importantly, as described in a later section, there is a very intimate interplay between the tumor and the immune cells that infiltrate and surround it, which drastically shape cancer progression, defining the balance between tumor escape and elimination (Schreiber et al., 2011). Lipid mediators are another factor of the TME, which can stimulate angiogenesis, enabling tumor growth and survival. These include LPA, which stimulates the production of the angiogenic cytokine IL-8, and PGE_2, which can enhance angiogenesis through the induction of vascular endothelial growth factor (VEGF) production (Hisano and Hla, 2019). PGE_2 also strongly influences the immune compartment within the TME, leading to a pro-tumorigenic state, as explained in a later section. In some cases, the mechanisms in which tumors exploit their TME for their own benefit are more intricate. For example, in pancreatic ductal

adenocarcinoma (PDAC), pancreatic stellate cells are induced to transdifferentiate into activated cancer associated fibroblasts, which secrete lysophosphatidylcholines (LPCs) (Auciello et al., 2019). PDAC cells then use these LPCs to support their membrane synthesis and also express autotaxin, which converts LPC into LPA. This LPA promotes AKT signaling, proliferation and migration of human and murine pancreatic cancer cells *in vitro* (Auciello et al., 2019). *In vivo*, inhibition of autotaxin reduced AKT signaling and tumor growth in mouse orthotopic PDAC models (Auciello et al., 2019). In summary, not only does the synthesis and metabolism of lipids play a role in tumor growth and development, but also the signaling molecules that are downstream can define interactions between different cell types in the TME (**Figure 2**).

Heterogeneity in tumor lipid metabolism

The dysregulated metabolic phenotypes and mechanisms described above are not common to all cancers types but they evidence an inter-tumor and sometimes intra-tumor heterogeneity that can hinder the efficacy of therapeutic approaches (Strickaert et al., 2017). One example of inter-tumor lipid metabolism heterogeneity is ACACA. Its inhibition in breast cancer stimulated epithelial-to-mesenchymal transition and metastasis (Rios Garcia et al., 2017), while ACACA and ACACB inhibition decreased cell proliferation in other tumor types, such as glioblastoma (Jones et al., 2017). Another example is the *FASN* gene, as its elevated expression correlated with advanced stages of colorectal cancer and liver metastasis, and its inhibition reduced metastasis of human colorectal cancer cells in athymic nude mice (Zaytseva et al., 2012). Paradoxically, *FASN* knockdown in a human lung cancer cell line led to increased metastasis and lower survival of NOD/SCID mice (Jiang et al., 2015). Similarly, in B16F10 melanoma-derived tumors, lung fibroblast-secreted cathepsin B (CTSB) induced the upregulation of SCD1, and SCD1 inhibition impaired lung metastasis formation (Liu et al., 2018). In contrast, while microphthalmia-associated transcription factor (MITF)-high melanoma cells require SCD for proliferation, the MITF-SCD axis suppresses metastasis, inflammatory signaling, and an ATF4-mediated feedback loop that maintains de-differentiation (Vivas-García et al., 2020). These examples highlight the importance of tailoring therapeutic approaches targeting cancer metabolism to specific tumors considering their different metabolic phenotypes. Interestingly, lipid heterogeneity is also observed within a tumor, as shown by mass spectrometry imaging and immunohistochemistry of human breast cancer xenografts (Cimino et al., 2013). Here, different phospholipids displayed specific distributions in areas of hypoxia, inflammation or proliferating tumor cells, indicating a certain biological distribution in tumor compartments relevant for tumor evolution and response to treatment; while other phospholipids were associated with tumor type and/or invasiveness (Cimino et al., 2013).

Cancer cell signaling and lipids

Although the role of lipid metabolism downstream of oncogenic pathways is appreciated (Harayama and Riezman, 2018; Snaebjornsson et al., 2020), the contribution of lipid metabolism in regulating oncogenic signaling is emerging. Here, we summarize recent key advances in understanding how lipid metabolism supports cancer growth and development.

Interactions between lipids and signaling pathways

Oncogenic signaling pathways and lipid metabolism are intimately linked. For example, changes in plasma membrane dynamics is a well-established means by which cancer cells can affect the clustering of cell surface receptors, such as receptor tyrosine kinases (Irwin et al., 2011). Specifically, the concept that lipid rafts, sphingolipid and cholesterol-rich plasma membrane microdomains, can aid receptor clustering and downstream oncogenic signaling is well established (Lingwood and Simons, 2010; Sezgin et al., 2017). However, emerging evidence showed that membrane FA remodeling also contributes to this phenomenon, maintaining the dynamic turnover of lipids. Here, the Lands cycle involves the concerted cooperation of phospholipases and LPC acyltransferases (such as LPCAT1) to hydrolyze FA from phospholipids, generating remodeled phospholipids from the resulting lyso-phospholipid (Lands, 2000). Recent work in glioma models showed that LPCAT1-mediated Land's

cycle leads to membrane PC saturation, which in turn enhances EGFR clustering and downstream signaling (Bi et al., 2019) (**Figure 3**). At the same time, a separate study showed that ELOVL2, which preferentially elongates long chain PUFA species (Leonard et al., 2002), promotes EGFR clustering and signaling (Gimple et al., 2019). Taken together, several factors including membrane order, sphingolipid and cholesterol content, the profile of FA moieties on membrane phospholipids, and the enzymes responsible for synthesizing these lipid species can significantly affect oncogenic signaling.

YAP and TAZ are critical mediators of the Hippo pathway, play important roles as mediators of oncogenic signaling and cell attachment, and are intimately intertwined with lipid metabolism. Specifically, YAP/TAZ activity is in part driven by SREBP-2 (Sorrentino et al., 2014), and are in turn stabilized and localized to the nucleus by lipogenic enzymes such as SCD1 (Noto et al., 2017). Whereas YAP/TAZ promotes survival in attached epithelial cells, in mesenchymal cells they promote pro-ferroptosis signaling pathways and sensitivity to ferroptosis-mediated cell death (Wu et al., 2019; Yang et al., 2019, 2020). Indeed, removal of TAZ can confer ferroptosis resistance (Yang et al., 2020). This may in part explain the exquisite sensitivity to ferroptosis of often therapy resistant mesenchymal cells by the inhibition of the lipid bilayer penetrating glutathione dependent enzyme glutathione peroxidase 4 (GPX4). While lipid metabolism is classically considered important to cancer cells for the contribution to membrane biomass production, this view is expanded by recent findings showing that it plays pivotal roles in cell signaling and ROS tolerance as outlined above, especially when considering recent work linking metastatic dissemination with lipid metabolism and ROS tolerance and metastasis resistance in cancer (Ubellacker et al., 2020).

Ferroptosis interactions with lipid metabolism in cancer cells

Ferroptosis is a newly discovered mechanism of cell death driven by iron-dependent lipid hydroperoxide formation (Dixon et al., 2012). In this process, oxygen radicals are formed from hydrogen peroxide (H_2O_2) via the Fenton reaction, which can peroxidize neighboring PUFA moieties present in membrane phospholipids (Dixon et al., 2012; Yin et al., 2011). GPX4 is a key enzyme in ferroptosis, reducing lipid peroxides via reduced glutathione and is a key regulator of ferroptosis in cancer cells (Yang et al., 2014). Largely due to the glutathione requirement for GPX4 function, the cystine/glutamate antiporter, solute carrier family 7 member 11 (SLC7A11, or xCT), is a critical component of the glutathione generating machinery that GPX requires. Limiting glutathione levels or GPX4 function leads to a toxic accumulation of lipid hydroperoxides (Yang et al., 2014). Accordingly, SLC7A11 was shown to promote survival in several cancer models including triple negative breast cancer and liver cancer (Ji et al., 2018; Robert et al., 2015; Timmerman et al., 2013; Yang et al., 2018). Besides GPX4, reduced ubiquinone is a potent cellular antioxidant (Frei et al., 1990) that can provide ferroptosis tolerance, even in cells that lack GPX4. Myristoylation of the enzyme ferroptosis suppressor protein 1 (FSP1) can regenerate ubiquinol from ubiquinone in a NADPH dependent manner, a process that is analogous to the glutathione-GPX4 axis (Bersuker et al., 2019; Doll et al., 2019). Critically, inhibiting both GPX4 and FSP1 in lung cancer cell line xenograft models sensitized them to ferroptosis, highlighting the translational potential of this approach (**Figure 4**). While modulation of the antioxidant capacity of the cell is an obvious target to affect ferroptosis, lipid metabolism plays a large role in determining cell sensitivity to this process.

Given the specificity for PUFA-phospholipids in ferroptosis, a possible means for cancer cells to protect themselves is simply by the depletion of membrane PUFA, as supported by evidence in *Drosophila*¸ breast cancer, fibrosarcoma and prostate cancer cells (Bailey et al., 2015; Doll et al., 2017; Magtanong et al., 2019; Rysman et al., 2010). Elevating *de novo* lipogenesis and increasing SFA and MUFA production is a method for depleting ROS labile PUFA from membranes, enhancing their resistance to lipid peroxidation (**Figure 4**) (Rysman et al., 2010; Talebi et al., 2018). The spatial distribution of PUFA can have critical importance protecting them from ROS sources. Specifically, whereas phospholipids are readily accessible to ROS, TAG are relatively inert (Bailey et al., 2015). PUFA can be stored in TAG in times of oxygen stress, thereby leading to membrane PUFA depletion and protecting the cell from ROS (Bailey et al., 2015). An analogous process is well established in which TAGs can act as a

FA store, which can be released under met conditions. Specifically, renal cell carcinoma cells store MUFA in TAGs, which is required to maintain membrane integrity in hypoxia where MUFA generation is limited (Ackerman et al., 2018). In this way, TAGs likely play a critical but unappreciated role in buffering membrane composition.

Conversely, PUFA availability is dependent on lipid uptake into the cells since essential FA are required for PUFA synthesis (Lee et al., 2016). This mechanism has been explored further, focusing on the ACSL family of enzymes which generate FA-CoA conjugates, a critical step that is required in further derivatization of FA. Without their activity, FFA cannot be incorporated into membrane lipids. In a screen of cells lacking GPX4, ACSL4 knockout cells showed remarkable resistance to ferroptosis (Doll et al., 2017). ACSL4 is specifically required to conjugate PUFA species, and its loss of function reduces membrane lipid poly-unsaturation. Conversely, ACSL3 was shown in human fibrosarcoma cells to conjugate both PUFA and MUFA, and in the context of conjugating exogenous MUFA into membrane lipids, it plays key roles in conferring ferroptosis resistance (Magtanong et al., 2019). Further, in the *in vivo* setting, metastatic melanoma cells in the oleate-rich lymph environment were also found to utilize oleate to protect themselves from ferroptotic cell death, an effect that was ACLS3 dependent (Ubellacker et al., 2020). In this way, by regulating the activity of ACSL enzymes, cancer cells can exert a measure of control over the saturation degree of their membrane (**Figure 4**).

In contrast to the role of ACSLs in modulating ferroptosis sensitivity, the role of other membrane lipid remodeling enzymes such as LPCATs and phospholipases (PLAs) remains obscure. For example, LPCAT enzymes are required to generate phospholipids by the condensation of a lysophospholipid and a FA, and they have varied specificities with respect to the preference for phospholipids and FA. LPCAT1 preferentially generates saturated PC species (Bi et al., 2019), whereas LPCAT3 can generate AA containing phospholipids (Hashidate-Yoshida et al., 2015). Much like ACSL enzymes, it is possible that LPCATs can regulate ferroptosis sensitivity in cells by altering the amount of membrane MUFA and PUFA. PLAs exert an opposite role to LPCAT enzymes by hydrolyzing phospholipids to generate a lysophospholipid species and an FA, and are critical in the dynamic process of membrane remodeling. Cytosolic PLA enzymes and certain secreted PLA type A2 (PLA2) enzymes have been implicated in preferentially cleaving PUFA, such as AA, from membranes (Sato et al., 2020). In doing so, it is possible that specific PLAs can deplete PUFA from membranes rendering the cells ferroptosis resistant. This concept is very recently evidenced in a model of renal failure, placental trophoblastic tissue and in models of Parkinson's disease (Beharier et al., 2020; Friedmann Angeli et al., 2014; Sun et al., 2021). However, the role of PLA2s in cancer remains largely unexplored.

Another mechanism to alter ferroptosis susceptibility is though altering the cells antioxidant capacity. An early study identified that FAO-derived NADPH in oxidative phosphorylation-high B cell lymphoma cells is required for maintaining ROS tolerance (Caro et al., 2012). Independent from FA metabolism, several key studies have shown the importance of the mevalonate pathway in enhancing the cell antioxidant potential (Bersuker et al., 2019; Doll et al., 2019; Garcia-Bermudez et al., 2019). Some anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphomas are auxotrophic for cholesterol as they lack squalene monooxygenase, and therefore rely on cholesterol uptake (Garcia-Bermudez et al., 2019). Critically, these cells were enriched in the normally undetectable hydrocarbon squalene which conferred robust ferroptosis resistance in cells and in patient-derived xenograft (PDX) models, highlighting both the role of squalene as an endogenous antioxidant and a targetable strategy in these cancers (Garcia-Bermudez et al., 2019).

Although ferroptosis is emerging as a very attractive antineoplastic target, there are myriad potential escape mechanisms that the cancer cell can exploit to become resistant. However, as many of these mechanisms rely on metabolic alterations which are measurable, this highlights the high potential of metabolic biomarkers working in concert with a rational ferroptosis inducing strategy. Moreover, the redundancy of escape mechanisms may well be positive as it may alleviate side effects on healthy tissue.

Lipid Metabolism Supporting the Metastatic Process: Dietary Influences and New Mechanisms

For most solid tumors the current therapeutic modalities (chemotherapy, radiation, and surgery) are efficient at treating primary tumors. Despite this success, the dissemination and establishment of cancer cells in secondary organs is the cause of a majority of cancer-related deaths (Dillekås et al., 2019). The metastatic process is challenging and inefficient, with few cells surviving extravasation and entry to the circulation (Fidler, 1970). Lipid metabolism is involved in cancer metastasis, and recent work has provided new insights on this process and the microenvironments that can support metastatic cells.

A first consideration for the role of lipids in metastasis, is the effect of lipid rich diets. Clinically, several cancers are associated with diet and obesity, including breast and colorectal cancer (Dong et al., 2017; Kyrgiou et al., 2017). Murine models of cancer have been used to directly test the effects of HFD feeding on metastatic disease progression, an inherently challenging association to study in clinical populations. Using mouse models of breast and colorectal cancer, HFD exposure has been shown to increase metastasis. In 4T1 murine metastatic breast cancer tumors, HFD increased primary tumor growth, and elevated metastasis to lymph nodes and bone marrow (Evangelista et al., 2019). In a model of hormone-sensitive breast cancer, HFD increased total numbers of metastases, regardless of primary tumor size, suggesting that metastatic potential stimulated by HFD is independent of primary tumor growth kinetics (Bousquenaud et al., 2018). Diet-induced obesity was a requirement for this effect, with obesity-resistant mice not experiencing increased metastatic tumor growth with HFD-feeding (Bousquenaud et al., 2018). Using the CR26 colorectal cancer cell line, feeding BALB/c mice with a choline-deficient HFD stimulated fatty liver development and increased liver metastases (Masaki et al., 2020).

Recent evidence supports non-canonical impacts of lipid availability on cancer metastasis, including immune cell modulation and lipid uptake regulation. For example, in a model of breast cancer metastasis, HFD was shown to increase total numbers and markers of activation and mobilization neutrophils in lungs from HFD-fed mice (Quail et al., 2017). Similarly, a cholesterol-rich diet and the metabolite 27-hydroxycholesterol was found to stimulate myeloid cell function, and was a requirement for breast cancer metastatic growth (Baek et al., 2017). HFD can also increase the ability of cancer cells to take up lipids to impact metastasis development. Recent work shows HFD feeding increased CD36 expression and was associated with increased lung metastases in a mouse model of gastric cancer, and squamous cell carcinoma metastases (Jiang et al., 2019; Pascual et al., 2017). This suggests that cancer cells in a lipid-enriched environment can be rewired to increase uptake, thus supporting further cell growth mechanisms. These are two newly discovered mechanisms of how increased lipid availability can impact cancer metastases.

Lipid uptake and storage as a mechanism of surviving cellular stress

Lipid uptake and storage has emerged as an important metabolic adaptation supporting metastasis, with proposed mechanisms being independent from strict energy supply for the cell. CD36 was identified as an important mediator for lipid-driven metastatic cell adaptation for survival (Pascual et al., 2017). Here, CD36 expression in oral squamous cell carcinomas drove metastatic formation, and treatment with anti-CD36 antibodies inhibited metastatic formation, causing full remission, eliminating lymph node and lung metastases in the Ln7 oral cancer model (Pascual et al., 2017). Similar effects were also reported in ovarian cancer cells (Ladanyi et al., 2018). Further work on CD36 in gastric cancer provided evidence that AKT activation and NFκB activation are involved in CD36 expression, linking lipid uptake and cell signaling pathways (Jiang et al., 2019; Pan et al., 2019). One common outcome of increased lipid uptake is the formation of LD (Ladanyi et al., 2018; Pascual et al., 2017). While LD are classically described as storage depots for cellular lipids to be released and oxidized for energy during starvation, they also play an important role in mediating ROS production. LD accumulation could act as a priming phenotype to prepare for metastasis, with both energy storage and ROS regulation mechanisms playing a role. Indeed, recent work found a direct mechanism linking KRAS oncogene expression and LD metabolism in pancreatic cancer, which is highly metastatic (Rozeveld et al., 2020). HSL was shown to be a key regulator of metastatic potential, and upon inhibition by KRAS, LD accumulation and metastasis was increased (Rozeveld et al., 2020). Pancreatic cancer metastases were found to have decreased LD,

suggesting that lipolysis and oxidation of stored lipids provided a mobile battery to support disseminated cells (Rozeveld et al., 2020).

The TME has also been shown to impact lipid uptake and influence the metastatic process. For example, acidity of the microenvironment was found to play an important role in CD36 and DGAT expression, and LD formation in in colorectal, cervical, and squamous cell carcinoma cancer cells (Corbet et al., 2020). Low pH-adapted cells had increased surface CD36 expression, leading to LD accumulation in a TGFβ2-dependent manner, and colorectal cancer cells that had elevated metastatic capacity (Corbet et al., 2020). In gastric cancer metastases, high lipid content in the peritoneum was found to upregulate DGAT2, LD formation, and mediate ROS production (Li et al., 2020a). Adipocytes in the local environment can also influence metastatic potential. For example, ovarian cancer cells co-cultured with adipocytes had increased LD formation, decreased ROS levels, and elevated lipogenic proteins (Ladanyi et al., 2018; Mukherjee et al., 2020). The lipid chaperone protein FABP4 was involved in these effects, with decreased expression leading to reduced metastasis and enhanced sensitivity to chemotherapy (Mukherjee et al., 2020). Hypoxia inducible factor 2α (HIF-2 α) may also be involved with LD formation in metastasis. HIF-2α in TNBC cells was found to be critical for mediating lipid storage and metastatic burden, with HIF-1α not driving an effect (Shah et al., 2015). Overall, evidence suggests that LD formation is a common phenotype across various cancer types, with a number of mechanisms that are involved in supporting metastasis (**Figure 5**).

Lymph node lipid metabolism and metastatic support

The lymph nodes are an important microenvironment supporting the metastatic process by attenuating ROS in metastatic cells. In metastatic melanoma, elevated ROS in circulating cells and subsequent metastatic potential has been described for some time, and understanding the delicate balance for ROS production in promoting survival signals versus driving cell death remains an active area of cancer research (Piskounova et al., 2015; Tasdogan et al., 2020). Recent work in these models found metastatic cells that passed through the lymphatic system, but not cells entering directly to systemic circulation, had upregulated FA metabolic pathways, and were enriched in oleic lipid species, supplied by the oleate-rich lymph fluid (Ubellacker et al., 2020). Here, melanoma cells that passed through the lymph had reduced ROS and ferroptosis, and the protective effects of oleic acid relied on *Acsl3* gene expression (Ubellacker et al., 2020). Further, the authors suggest that elevated ferroptosis in circulating tumor cells could be a result of the iron-rich environment of the blood, and cells passing through lymph can be protected from ferroptotic cell death during the metastatic process (Ubellacker et al., 2020). Additional work on B16F10 melanoma cells growing as micro- and macrometastases in lymph nodes had upregulated transcriptomes for FAO and bile acid metabolism (Lee et al., 2019). Here, lymph fluid and metastatic cells in the lymph nodes had elevated lipid profiles, and the presence of bile acids activated YAP signaling to support and drive metastatic cell survival and growth (Lee et al., 2019). Interestingly, the authors commented on a possible autocrine mechanism, with metastatic melanoma cells potentially biosynthesizing the bile acids used to drive the survival signaling of the YAP pathway, an area requiring further exploration. Together, these studies highlight an important consideration for the biology of metastasis and the route to circulation, with the evidence suggesting that enhanced metastatic survival is possible if circulating tumor cells undergo a metabolic "processing" through lymph tissues prior to entering systemic circulation (**Figure 5**).

Lipids in cancer-related immunometabolism

Metabolic reprogramming of immune cells

Along all phases of tumor progression, there is a constant interplay between the tumor and the immune compartment of the TME. These immune cells can be tumor-suppressive or tumor-promoting (Schreiber et al., 2011) and their lipid metabolism is often reprogrammed in cancer, which can tip the balance towards tumor immune escape. $CD4^+$ and $CD8^+$ T cells occupy a central role in the defense against cancer development, and undergo a physiological metabolic reprogramming during their path from

naïve to effector and memory T cells. Effector T cells rely mainly on aerobic glycolysis for energy, but other stages of T cell differentiation shift towards lipid metabolism (Wang and Green, 2012). Such is the case for naïve, memory and also the immune suppressive regulatory T cells (Tregs), which rely mainly on FAO as an energy source (Michalek et al., 2011; O'Sullivan et al., 2014; Wang and Green, 2012). Furthermore, activated T cells are unable to grow and proliferate with loss of SREBP signaling due to the lack of cholesterol availability (Kidani et al., 2013). Membrane cholesterol levels can regulate T cell receptor (TCR) clustering and the formation of the immunological synapse, modulating T cell function and signaling (Yang et al., 2016). In the myeloid compartment, dendritic cells (DCs) are antigen presenting cells that are crucial for the activation of tumor specific T cell responses. Immature bone marrow derived DCs rely on FAO and oxidative phosphorylation, but become glycolytic and lipogenic upon activation, and progresses to a commitment to aerobic glycolysis (Giovanelli et al., 2019). Beyond these physiological DC phenotypes, a study using monocyte-derived human DCs showed that tolerogenic DCs, which are associated with immune suppression and present reduced functionality, rely on high levels of FAO and oxidative phosphorylation but also glycolysis (Malinarich et al., 2015). Furthermore, tolerogenic DCs with upregulated levels of FAO supported immune suppression in mice and were important for tumor progression in an *in vivo* murine melanoma model (Zhao et al., 2018). Tumor associated macrophages (TAMs) are another relevant immune player in the TME, which can exist in a wide range of phenotypes. Two oppositional macrophage polarized states are classically defined: the pro-inflammatory M1 state associated with tumor suppression, and the healing/growth promoting and tumor-promoting M2 state (Italiani and Boraschi, 2014). A study employing human and murine macrophages showed that while M1 macrophages primarily rely on aerobic glycolysis, the M2 type use FAO and are dependent on lipid uptake and lysosomal lipolysis to be activated (Huang et al., 2014). Chronic inflammation also leads to the accumulation myeloid derived suppressor cells (MDSCs), which are immature cells that mediate immune suppression in the TME through various mechanisms (Groth et al., 2019). As in the case of TAMs, MDSCs can show a spectrum of metabolic phenotypes that include glycolysis, FA synthesis and FAO. Although there is evidence supporting that FAO is predominant in tumor-infiltrating MDSCs in certain cases (e.g. using a murine lung cancer model and biopsies from patients with colon, renal, and breast cancers (Hossain et al., 2015)), it is not yet completely clear which the preferred metabolic state of these cells in the TME is (Yan et al., 2019). In summary, distinct immune cell types have very different metabolic programs and these cells also experience a metabolic reprogramming that changes throughout their differentiation and activation processes.

Interplay between the tumor and the immune cell compartment of the TME

Given the varied metabolism of immune cells and along their differentiation stages, nutrient availability could influence immune cell composition and function in the TME and, therefore, tumor immune evasion, which is a hallmark of cancer development (Hanahan and Weinberg, 2011). Interestingly, evidence suggests that many tumor-promoting immune cells can survive in a low-glucose TME, while most of their tumor-suppressive counterparts compete with the tumor for glucose. For instance, through glucose nutrient competition and checkpoint molecule interactions, murine sarcoma tumors can impair effector T cell metabolism and function (Chang et al., 2015). Similarly, a study using Jurkat cells, murine T cells and melanoma models showed that the glycolysis metabolite phosphoenolpyruvate plays a key role in Ca^{2+}-NFAT signaling in T cells allowing antitumor responses, uncovering a mechanism in which a glucose-poor environment can hamper T cell effector function (Ho et al., 2015). Conversely, certain tumor-promoting immune cells can rely on other nutrients and may not be affected by this competition. This includes Tregs, M2 macrophages, MDSCs and tolerogenic tumor infiltrating DCs, which have been reported to use FAO (Hossain et al., 2015; Huang et al., 2014; Malinarich et al., 2015; Michalek et al., 2011; Zhao et al., 2018). At the same time, tumor cells can increase FA synthesis to sustain their growth (Röhrig and Schulze, 2016), leading to a high lipid content in the TME. Tregs and M2 macrophages largely rely on FAO and take up exogenous FA (Berod et al., 2014; Huang et al., 2014), thus, an increase in FA availability in the TME could aid in these cells' development. Supporting this hypothesis, a study employing samples from lung cancer and melanoma patients, and colon cancer and melanoma murine models reported that intratumoral Tregs show an enhanced FA uptake and, in certain tumors, also increased lipid accumulation (Wang et al., 2020). Furthermore, CD36 was upregulated in intratumoral

Tregs and it is a central metabolic modulator in these cells (Wang et al., 2020). Lipids also impact cytotoxic natural killer (NK) cells, innate immune cells that play an important role in the antitumor response (Miller and Lanier, 2019). The cytokine-mediated activation of these cells leads to increased glycolysis and oxidative phosphorylation (Assmann et al., 2017). In melanoma and colorectal cancer surgical models and in colorectal cancer patient samples, NK cells showed increased lipid accumulation in the postoperative period, associated with enhanced expression of scavenger receptors (e.g. MSR1, CD36, CD68) and inhibition of NK cells cytotoxic function against tumor cells (Niavarani et al., 2019). The increased FA uptake in NK cells from melanoma-bearing mice suggests that these upregulated receptors are responsible for the effects observed (Niavarani et al., 2019). Another study employing murine models reported that obesity brings about a peroxisome-proliferator activated receptor (PPAR)-mediated lipid accumulation and metabolic reprogramming towards lipid metabolism in NK cells (Michelet et al., 2018). This was associated with the overexpression of genes such as *Ldlr*, *Cd36*, genes encoding FABPs and *Cpt1b*. These NK cells downregulated glycolytic metabolism and their antitumor function was inhibited, and these results were supported by data from obese human patients. Moreover, lipid-treated NK cells were unable to reduce melanoma tumor growth in mice, and NK cells in tumors of obese mice were functionally impaired (Michelet et al., 2018). Similarly, a high concentration of FA in the TME was correlated with the accumulation of LDs in TAMs, acting as reservoirs of ligands for PPARβ/δ, whose activation upregulated genes associated with pro-tumorigenic human TAM polarization in ovarian carcinoma (Schumann et al., 2015). Tumor associated DCs are also affected by lipid accumulation, which can impair their function by decreasing antigen presentation, as shown in different cancer types (Herber et al., 2010). In human samples and mouse models of ovarian cancer, lipid accumulation was associated with DC ER stress (Cubillos-Ruiz et al., 2015). Furthermore, MDSCs in cancer patients and tumor bearing mice were found to have higher lipid accumulation, enhanced FA uptake, and increased immunosuppressive function (Hossain et al., 2015; Yan et al., 2019). In a murine model of pancreatic cancer, dysfunctional $CD8^+$ T cells increased their uptake and accumulation of specific long-chain FA, which led to T cell dysfunction, inhibition of mitochondrial function, reduction of FA catabolism and lipotoxicity (Manzo et al., 2020). Cholesterol can also be enriched in the TME and induce $CD8^+$ T cell ER stress, leading to inhibitory immune checkpoint molecules expression and exhaustion (Ma et al., 2019), although this lipid is necessary in certain levels for normal T cell effector function (Kidani et al., 2013; Yang et al., 2016). All these examples illustrate how FA and cholesterol in the TME could be supporting a tumor-promoting microenvironment **(Figure 6)**. Interestingly, murine colorectal cancers in HFD-fed mice were recently shown to increase lipid uptake, starving and impairing tumor infiltrating T cells (Ringel et al., 2020), showing that certain level of lipids are required for antitumor T cell function.

Tumor cells can also disrupt the immune response via secretion of lipid-derived signaling molecules to the TME. For example, PGE_2 suppresses immune responses mediated by T helper 1 (Th1) cells, cytotoxic T lymphocytes and NK cells; while at the same time promoting Th2 and Th17 responses, Tregs and MDSCs (Groth et al., 2019; Kalinski, 2012) as well as promoting the polarization of murine macrophages to the M2 pro-tumorigenic phenotype (Luan et al., 2015). These immune cell modulations culminate to create an ideal environment for tumor progression and these findings show that lipid-derived signaling molecules also play a role in the complex interactions between tumor cells and immune cells within the TME.

Immune checkpoint inhibitors affecting lipid metabolism

Immune checkpoint blockade therapies have represented a turning point in the history of cancer treatments, leading to long lasting clinical responses that had never been achieved before (Sanmamed and Chen, 2018). This approach uses monoclonal antibodies against inhibitory receptors on the T cell surface, most prominently programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), to block these immune breaks and unleash T cells' antitumor function (Sanmamed and Chen, 2018). A study using human primary $CD4^+$ T cells showed that while CTLA-4 ligation inhibits glycolysis without affecting FAO, the interaction of PD-1 with its ligands inhibits glycolysis and amino acid metabolism while increasing FAO (Patsoukis et al., 2015). Similar results were found in an *in vivo* murine model of chronic viral infection, where exhausted $CD8^+$

T cells exhibited inhibited glycolytic and mitochondrial metabolism regulated by PD-1, while at the same time upregulating FAO (Bengsch et al., 2016). Anti PD-L1 (a PD-1 ligand) antibody treatment reversed these metabolic alterations and reinvigorated a subpopulation of exhausted T cells (Bengsch et al., 2016). Thus, it could be speculated that the shift towards FAO in exhausted T cells could be critical for their extended survival in the TME to allow for reinvigoration with antibodies targeting PD-1 or its ligand. Interestingly, a study employing murine ovarian and melanoma tumor models, a human melanoma cell line and human fibrosarcoma xenografts showed that upon checkpoint blockade treatment, in addition to specifically killing tumor cells, reinvigorated $CD8^+$ T cells sensitized cancer cells to ferroptosis through a process triggered by secreted IFNγ (Wang et al., 2019). In conclusion, lipid metabolism is an important aspect of cancer immunotherapies mechanisms of action, which opens new possibilities for the improvement of these treatments as described in a later section.

Targeting lipid metabolism for cancer therapy

An appealing approach to enhancing current cancer therapies is to combine well known, cheap, and easily tolerated metabolic therapies in addition to conventional treatment modalities. This is the case for a number of metabolic drugs used to treat common diseases, such as type 2 diabetes (Rao et al., 2018; Saif et al., 2019) and cardiovascular disease (Farooqi et al., 2018; Wang et al., 2016a). The pathology of these diseases also involve dysregulated lipid metabolism, so therapies targeting these common pathways could provide opportunities to use them for cancer therapy. For example, statins, a class of drugs that inhibits HMGCR and cholesterol synthesis are clinically used to treat cardiovascular disease, and are actively being studied for anticancer effects with almost 30 currently recruiting clinical trials registered on clinical trials.gov for multiple types and stages of cancer (as recently reviewed (Longo et al., 2020)). Further, therapies for metabolic disorders that failed clinical trials due to negative side effects are also an opportunity for repurposing for cancer therapy. An example of this is phenformin, a type 2 diabetes therapy discontinued due to risk of lactic acidosis, has been reassessed for cancer therapy potential (Rubiño et al., 2019). In essence, by inhibiting lipid metabolism in certain tumor environments, a situation could be created where either the cells experience impaired growth, lipids used for energy are depleted, or ROS levels are enhanced, elevating the sensitivity to further stress and increasing therapeutic response. The continued development of high-throughput screens for small molecule inhibitors have identified compounds in recent years that can offer enzyme inhibition with molecular target specificity. As the understanding of cancer metabolism progresses, novel targets involved in lipid metabolism continue to be discovered, providing potential opportunities for targeting unique enzymes and pathways that are preferentially elevated in cancer cells. Further, with the advent of cancer immunotherapies and immunometabolism, additional opportunities for modulating lipid metabolism for an enhanced response to immune therapies have been presented.

Lipogenic enzyme-specific inhibitors: small molecule inhibitors at the forefront of targeted drug discovery

As the prospect of discovering a metabolic Achille's heel remains a tempting and promising venture, the development of small molecule inhibitors and drug screens for enzyme-targeted effects has allowed for continued study beyond the current well-known metabolic pharmaceuticals. Indeed, small and large pharmaceutical companies alike have spent considerable time and resources on developing novel therapies to target lipid metabolism for cancer treatment (**Table 1**, **Figure 7**)(Garber, 2016). Here, we describe the current landscape for inhibitors of lipid metabolism, pre-clinical evidence in cancer models, and any clinical trials or implications.

ACACA/ACACB

ACACA/ACACB can be phosphorylated and inhibited downstream of AMP activated protein kinase (AMPK) in response to low cellular energy, and AMPK activation for ACACA inhibition is well described and targeted (Steinberg and Carling, 2019). Small molecule inhibitors of ACACA and ACACB have been discovered and tested for their effects in cancer, with promising pre-clinical results.

In 2016, ND-646 was described to allosterically inhibit both ACACA and ACACB isoforms, and prevent the development of non-small cell lung cancer (NSCLC) (Li et al., 2019; Svensson et al., 2016). Another small molecule inhibitor, the liver-specific ND-654, was tested in a murine model of HCC development, and found to inhibit liver lipid synthesis, decreasing tumor formation (Lally et al., 2018). Both of these inhibitors were tested in combination with a standard of care chemotherapy (carboplatin for NSCLC and sorafenib for HCC), further inhibiting tumor size and incidence compared to monotherapy (Lally et al., 2018; Svensson et al., 2016). Few direct ACACA/ACACB inhibitors have translated to clinical trials, and those that have are currently under investigation, or their trials have recently been completed for metabolic diseases. Such is the case of the current testing of Firsocostat in non-alcoholic steatohepatitis (Alkhouri et al., 2020) (NCT02856555, NCT03987074), although translation of this agent for metabolic diseases is also facing challenges (Gliead Sciences, 2019).

FASN

FASN is an attractive target for inhibiting cancer cell proliferation, as its expression is often elevated in cancer cells, but most inhibitors to date have difficulty translating into clinical settings due to adverse effects (Flavin et al., 2010). However, drugs targeting FASN for treating obesity are clinically used, such as Orlistat (tetrahydrolipstatin). Orlistat was tested for anti-cancer effects, with preliminary work showing the drug inhibits prostate cancer tumors in mice (Kridel et al., 2004). Despite promising pre-clinical effects in murine models of cancer (**Table 1**)(Agostini et al., 2014; Carvalho et al., 2008; Dowling et al., 2009; Kridel et al., 2004; Seguin et al., 2012), clinical translation has been challenging and faces several pharmacological limitations to be used as a drug in circulation (Flavin et al., 2010). For example, orlistat does not appear to affect clinical development of colorectal cancer (Hong et al., 2013). Despite being an FDA-approved therapy, there are currently no registered clinical trials (listed on clinicaltrials.gov) to study orlistat and cancer, possibly due to low bioavailability and numerous off-target effects (Kridel et al., 2004). The exploration of new molecules through screens have been employed to find new potential compounds. For example, Sagimet Biosciences (formerly 3V-Biosciences) has focused specifically on testing FASN inhibitors, with early work showing beneficial effects against cancer growth in pre-clinical models (Ventura et al., 2015). The TVB-3166 and TVB-3664 compounds inhibited cancer cell growth and stimulated apoptosis by modulating the PI3K-Akt-mTOR pathway and β-catenin signaling, and altering lipid profiles (Ventura et al., 2015). These compounds were tested in combination with chemotherapies (paclitaxel, docetaxel) in colon and lung cancer xenografts, with sensitizing effects (Heuer et al., 2017). TVB-3664 was later validated in patient-derived xenografts of colorectal cancer (Zaytseva et al., 2018). Other compounds from this company (TVB-2640) are in clinical testing for various cancer types and in combination with the current standard of care therapies, including NSCLC (NCT03808558), oral cancer (NCT02223247), colon cancer (NCT02980029), breast cancer (NCT03179904), and astrocytoma brain cancer (NCT03032484). Fasnall, a tiophenopyrimidine, was discovered through a chemoproteomic platform for compound screening (Alwarawrah et al., 2016). It was found to inhibit cancer cell growth, increase apoptosis, alter cancer cell lipidomes, and inhibit breast cancer tumor growth in mice alone and in combination with carboplatin (Alwarawrah et al., 2016). Repurposed drugs are also proposed for FASN inhibition in cancer, including proton pump inhibitors .These drugs inhibit the thioesterase domain of FASN, and were discovered in a virtual screening library and later validated in pre-clinical models (Fako et al., 2015). One of these drugs, omeprazole, is currently under clinical trial for a number of cancer types including castration-resistant prostate cancer (NCT04337580), and breast cancer (NCT02595372), with completed trials for colorectal cancer (NCT02518373) and other solid tumors (NCT00420615, NCT01596647, NCT01517399).

ACLY

ACLY has a number of inhibitors, both natural and synthesized, many of which have been tested for anti-cancer effects in pre-clinical and clinical studies (as reviewed (Granchi, 2018)). It has also been a target for the development of small molecule inhibitors, with a recent small-molecule screen identifying a number of potential molecules. NDI-091143 is a small molecule recently characterized and found to

allosterically bind to ACLY, creating a conformational change in the protein structure, impairing citrate binding, and has yet to be tested in cancer models (Wei et al., 2019). ETC-1002 is an ACLY small molecule inhibitor currently under investigation for cardiac disease, with phase III clinical trials under way (Bilen and Ballantyne, 2016). It exists as a pro-drug form that is later modified in the liver (to ETC-1002-CoA) for its activity, which leads to reduction of low-density lipoprotein cholesterol (LDL-C), suggesting it has site-specific effects in the liver (Pinkosky et al., 2016). It is currently the most successful ACLY small molecule inhibitor, although its effects on cancer cells remain largely unknown. Interestingly, recent work examining fructose metabolism by the gut microbiome as a significant source of acetyl-CoA to support hepatic lipogenesis identifies an important consideration for the applicability and use of ACLY inhibitors (Zhao et al., 2020). In this context, the diet and gut microbiome may be an opportunity to bypass ACLY inhibition, specifically for liver and liver cancers, which would be exposed to gut microbiome-derived acetyl-CoA via portal vein circulation (Zhao et al., 2020). However, early mechanistic studies employed HepG2 liver cancer cells to discover ETC-1002 in the prodrug form can also activate AMPK, with inhibitory effects on lipogenesis via ACACA inhibition (Pinkosky et al., 2013). Considering the tissue specificity for prodrug activation, ETC-1002 could have implications for liver cancer and may warrant further study.

SCD

SCD inhibitors are relatively new, and several groups are working on identifying small molecule inhibitors for this lipogenic enzyme (Uto, 2016). A number of inhibitors have been identified and tested in pre-clinical models of cancer (as reviewed in (Tracz-Gaszewska and Dobrzyn, 2019)). Recent work has found that SCD1 inhibition can stimulate ferroptotic and apoptotic cell death in ovarian cancer (Tesfay et al., 2019). Here, SCD1 inhibition by the compounds MF-438 and CAY10566 caused changes in membrane phospholipid composition that drove apoptotic signaling and ferroptotic cell death (Tesfay et al., 2019). Further, SCD1 was identified as a key gene that was differentially expressed in bladder and clear cell renal cell cancers compared to normal tissues, and SCD inhibition with a small molecule inhibitor (A939572) impaired cancer cell proliferation (Piao et al., 2019; Von Roemeling et al., 2013). Recent work with the SCD inhibitor Cpd 3j (Merk Frosst) helped uncover a novel metabolic re-wiring of various cancer cell lines, showing an alternative lipid saturation pathway mediated by FADS2 (Vriens et al., 2019). Contrary to those findings, in a pre-clinical study using microphthalmia-associated transcription factor (MITF) positive B16-F1 melanoma cells treatment with A939572 SCD inhibitor decreased primary tumor growth but promoted lung metastasis (Vivas-García et al., 2020). Few inhibitors have translated into clinical trials, with none being currently explored for cancer effects. MK-8245 is an inhibitor that has been studied as a clinical type 2 diabetes treatment (NCT00972322), as it is a liver-specific inhibitor (Oballa et al., 2011). Similar to ACLY inhibitors, the tissue specificity for liver or lipid tissues is an important aspect of these small molecule inhibitors for the treatment of metabolic therapies, which has implications for their applicability for cancer therapy.

Lipid uptake and storage inhibition

As described above, cancer cells can preferentially uptake lipids to support biosynthesis, energy production, and to sequester lipid species in LDs for energy supply and ROS mediation. As such, targeting lipid uptake into cancer cells is also an attractive therapy option. Inhibition of CD36 has been explored in non-cancer fields, and it binds a multitude of ligands, including thrombospondin-1 (De Fraipont et al., 2001; Isenberg et al., 2007). Thrombospondin-1 bound to CD36 also has anti-angiogenic activity, providing a potential dual-action against cancer cell growth: inhibition of angiogenesis to limit blood and nutrient availability to a tumor, and competitive binding for CD36 (De Fraipont et al., 2001). A number of thrombospondin analogues are currently being tested for anti-cancer effects, including VT1021 (Vigeo Therapeutics), which is currently in phase I clinical trials for treatment against a number of primary tumors (NCT03364400). ABT-510 is another analogue that was tested in clinical melanoma; however, it failed to achieve positive outcomes as a monotherapy in a phase II trial (Markovic et al., 2007). Interestingly, in recent work using anti-CD36 antibodies, the anti-cancer effect of CD36 may not be driven by thrombospondin interactions with CD36, particularly in the context of metastatic cancer.

CD36 inhibition by two different antibodies, FA6.152 which inhibits all CD36 activities, and JC61.3 which inhibits only FA and LDL protein uptake, were both found to be highly effective and specific for metastatic tumors in the lymph nodes (Pascual et al., 2017). Here, FA6.152 was able to inhibit both primary and secondary tumor development, whereas JC61.3 very strongly inhibited just secondary lymph node metastatic tumor development in a model of oral cancer. JC61.3 has been tested in pre-clinical models of gastric cancer, and found to inhibit *in vitro* cell migration and *in vivo* metastasis in oral and gastric cancers (Jiang et al., 2019; Pan et al., 2019). Further, the oleic acid analogue sulfo-n-succinimidyl oleate (SSO), which irreversibly binds CD36, was found to inhibit the pro-growth effects of co-culturing cancer cells with adipocytes or cancer-associated fibroblasts (Gong et al., 2020; Ladanyi et al., 2018; Yang et al., 2018). These studies highlight the importance of CD36 expression in cancer cells to respond to the TME, particularly in the context of FA availability. Taken together, these studies show that CD36 is potentially a very important target, and re-visiting thrombospondin-1 anti-angiogenic therapies within the specific context of metastatic seeding and formation should be further explored.

Lipid storage is an emerging and important mechanism that can affect cancer cell survival and metastatic processes, as described above. In recent years, targeting the DGAT enzymes responsible for generating TAG species, which are then stored in LD, has become an interesting target for obesity and type 2 diabetes treatments. As such, a number of companies have screened and developed drugs specific for DGAT1 (A922500, AZD3988, AZD7687) and DGAT2 (PF-06424439, JNJ-DGAT2-A and -B) enzymes. DGAT1 inhibition by A922500 was used in cervical cancer cells and liver cells, and shown to decrease TAG and LD synthesis (Corbet et al., 2020; Qi et al., 2012). Interestingly, impaired LD formation by A922500 was found to reduce cervical cancer cell invasion (Corbet et al., 2020). AZD3988 was also recently tested in prostate cancer cells, and pre-treatment of the inhibitor sensitized the cells to palmitate-induced cell death (Balaban et al., 2019). The third inhibitor, AZD7687 was the only compound of this group to undergo human clinical testing, where it was successful in decreasing circulating TAG, albeit with some significant gastrointestinal side effects (Denison et al., 2014). DGAT2 inhibition by PF-06424439 has been tested in pre-clinical models, where it decreased LD formation and metastasis in *in vitro* and *in vivo* testing in gastric cancer (Li et al., 2020a). It was also shown to sensitize breast cancer cells to chemotherapies (cisplatin, doxorubicin), but had no impact on colorectal cancer stem cells (Hernández-Corbacho and Obeid, 2019; Tirinato et al., 2019). These inhibitors largely remain to be tested in pre-clinical *in vivo* models; however, their development seems to be an active area for pharmaceutical companies for use in metabolic disorders. Their repurposing for cancer treatment is an interesting area, particularly with growing evidence for the biological role of LDs in cancer progression and survival.

Inhibitors of lipid oxidation for energy production

Inhibiting the ability of cancer cells to use FA as a source of energy is another potential therapeutic opportunity. As such, inhibiting lipid uptake into the mitochondria as means to limit energy production has been an attractive therapeutic target for many years (Ceccarelli et al., 2011). One of the most commonly used inhibitors of mitochondrial FAO in pre-clinical research is etomoxir, an irreversible CPT1 inhibitor. However, recent *in vitro* work has shown that concentrations used to achieve cell growth inhibition exceed that which is needed to inhibit >90% of CPT1 function, with off-target effects inhibiting complex I function, and high concentrations of etomoxir can deplete cellular CoA concentrations due to prodrug conversion to the active -CoA form (Divakaruni et al., 2018; Yao et al., 2018). Currently, clinical use of etomoxir is thought to be limited, with a past clinical trial on congestive heart failure halting due to toxic side effects (elevated liver transaminase) (Holubarsch et al., 2007). Nevertheless, etomoxir continues to be tested in pre-clinical models of cancer (Cheng et al., 2019a; Sawyer et al., 2020), and may be an option to revisit for cancer clinical trials. Reversible CPT1 inhibitors present an alternative with potentially less harmful side effects. For example, ST1326 is a reversible CPT1 inhibitor with anti-cancer effects found in several non-solid cancers (Gugiatti et al., 2018; Pacilli et al., 2013; Ricciardi et al., 2015). Other inhibitors of mitochondrial FAO are available, including perhexiline (CPT1 inhibitor) and trimetazidine (Mitochondrial long-chain 3-ketoacyl coenzyme A thiolase (LCTH) inhibitor, which catalyzes the final step in mitochondrial β-oxidation)) have some pre-clinical evidence in cancer models (**Table 1**), although all current registered clinical trials at

www.clinicaltrials.gov for these compounds are being tested for cardiac pathologies and type 2 diabetes. Should these compounds pass safety and scaling clinical trials, reconsidering their use for clinical oncology applications could be interesting.

Targeting lipid metabolism for cancer immunotherapy

Despite the success of immunotherapies, many patients cannot yet benefit from these treatments, or suffer from severe adverse effects caused by them (Sanmamed and Chen, 2018). Considering the central role played by lipid metabolism in immune cells function in the TME, targeting these pathways could be a strategy to improve immunotherapies efficacy. For instance, bezafibrate, a PPARγ co-activator-1α (PGC-1α)/PPAR complex agonist, synergizes with PD-1 blockade immunotherapy in mice, leading to an increased proliferation and survival of $CD8^+$ T cells (Chowdhury et al., 2018). This combination treatment induced a metabolic reprogramming in cytotoxic T lymphocytes with increased FAO, oxidative phosphorylation, and glycolysis (Chowdhury et al., 2018). Another study showed that uncoupling protein 2 (UCP2) expression in tumor cells is associated with an immunostimulatory TME, enhancing conventional DC type 1 and $CD8^+$ T cell antitumor responses. Here, the PPARγ agonist rosiglitazone, upregulates UCP2 in melanoma tumor cells, sensitizing tumors to PD-1 blockade, increasing survival in tumor bearing mice (Cheng et al., 2019b). Pharmacological inhibition of FAO in murine tumor models inhibited tumor-infiltrating MDSCs immune suppressive functions and delayed tumor growth, and this treatment synergized with the antitumor effects of T cell adoptive transfer therapy (Hossain et al., 2015). Another study reported that FAO inhibition with etomoxir in induced tolerogenic DCs also decreased tumor progression when these cells were transferred into melanoma tumor bearing mice. In this study, the treatment of tumor bearing mice with etomoxir led to tumor-suppressive effects and it synergized with the effects of anti PD-1 antibody therapy (Zhao et al., 2018). Recent work found that CD36 is an important metabolic modulator of intratumoral Tregs. Here, treatment of melanoma tumor bearing mice with anti-CD36 monoclonal antibodies led to Treg apoptosis and decreased accumulation in tumors, while $CD8^+$ T cell infiltration increased and tumor growth was reduced (Wang et al., 2020). The combination of this treatment with anti PD-1 therapy increased the antitumor response in two murine melanoma *in vivo* models, indicating that CD36 blockade could be used to enhance PD-1 blockade (Wang et al., 2020). In conclusion, there is mounting evidence that lipid metabolism regulation of the immune compartment of the TME holds great potential for the development of new treatments to synergize with current immunotherapies.

Conclusions and remaining questions

Altered lipid metabolism is now an undisputed factor in cancer metabolism. Here, we have discussed a number of new and emerging mechanisms for lipid metabolism supporting cancer growth and progression, potential targets of lipid metabolism in cancer, and therapies in testing for targeting and inhibiting cancer growth. However, recent findings in the areas of ferroptosis, immunometabolism and cancer immunotherapy, and the development of small molecule inhibitors identify gaps in our current knowledge. A dysregulated lipid metabolism is a key component in tumor metabolic adaptation, and helps to promote therapy resistance (Hangauer et al., 2017; Talebi et al., 2018; Tsoi et al., 2018), metastatic spread and secondary tumor growth (Ladanyi et al., 2018; Li et al., 2020a; Pascual et al., 2017). Furthermore, the local TME is an important aspect, with lipid availability or release from neighboring tissues present in both primary and secondary tumors (Mukherjee et al., 2020), further highlighting the importance of lipids throughout cancer development.

Current evidence shows that an altered lipid metabolism in the immune cells within the TME is commonly correlated to immune-suppressive and dysfunctional phenotypes. The reliance of these cells on TME-supplied lipids may allow them to thrive, while their tumor-suppressive counterparts are inhibited. This highlights the importance of investigating a broad spectrum of cellular targets for therapy, including the cells making up the TME, and the potential for combination treatments targeting lipid metabolism to reprogram the immune-suppressive microenvironment enhancing current cancer immunotherapies (Chowdhury et al., 2018; Hossain et al., 2015; Wang et al., 2020; Zhao et al., 2018).

This represents an interesting therapeutic approach, with the potential for one metabolic drug to have unexpected results by affecting different key cell populations within the TME at the same time. Overall, exploring the interplay between lipid metabolism and immune cell interactions within the context of cancer and the TME remains an area of great interest.

The mechanisms involved in lipid metabolism and cancer cell survival are an interesting and growing area of research. As highlighted here, cancer cells can preferentially sequester FA for energy storage and to prevent unwanted oxidation and ferroptosis. However, this is half of a delicate balance: increased PUFA in membrane lipids sensitizes to ferroptotic cell death, but high SFA can also cause lipotoxicity. In the context of metastasis, lipid metabolism seems to be a key, and targetable, factor in this process. Since the development of secondary tumors is the primary cause of cancer-related deaths, finding treatment opportunities that minimize this process is critical. Whether the effect lipids have on metastatic cancer cells is targeted directly to the cancer cells, as is the case of CD36-targeting therapies, or if using broader therapies that modulate the TME are an option requires further clarity and exploration for therapeutic exploitation. An important question that requires consideration, is the effect of the timing of lipid exposure during the process of cancer cell dissemination and spread to secondary tissues.

Overall, lipid metabolism in cancer is a topic that is far from over. In the light of the growing number of small molecule inhibitors that are increasingly better at tissue-targeted effects, there remain many opportunities for lipid-targeted therapeutic strategies that can have a translatable impact on their own or in combination with conventional or immune cancer therapies. Finally, the lessons we learn from lipid metabolism in cancer may be translatable to other diseases (**Box 1**) and may further guide our understanding of life style impact such as dietary habits in disease onset and progression.

Box 1: A Comment on Viruses and Lipid Metabolism in the Context of COVID-19

Oncolytic viruses initiate oncogenesis, and cause hundreds of thousands of cancer cases each year, such as hepatitis-driven liver cancer (de Martel et al., 2020). With the current global outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and the associated COVID-19 disease, understanding how viral infections and cancer intersect is of great importance. Viral infections can drive similar lipid metabolism re-wiring in infected cells to changes in cancer cells, and modulating lipid metabolism can impact viral entry, replication, egress, and infectivity (Ketter and Randall, 2019). Early results measuring blood lipid profiles from patients hospitalized with COVID-19 have shown decreased LDL and total cholesterol levels (Fan et al., 2020; Wei et al., 2020). This trend was found to persist, with LDL and high-density lipoproteins (HDL) dropping continuously from the moment of hospital admission to death associated with the infection (Fan et al., 2020). In a recent pre-print, results from severe COVID-19 cases suggest that HDL cholesterol is inversely related to disease severity and duration of stay in the hospital (Li et al., 2020b). While it is still early to understand distinct mechanisms of COVID-19 viral infection and cellular lipid changes, current clinical data suggest severe cases exhibit hypolipidemia, with cholesterol levels potentially providing a useful biomarker for disease progression. With the intense level of attention and focus that the global medical community is directing at SARS-CoV-2 and COVID-19, there rises the potential to execute well designed and organized retrospective studies to explore aberrations in lipid metabolism after infection, and, given common changes to lipid metabolism, the impact of a virus-driven lipid metabolism on the development of cancer over the long term.

Box 2: Abbreviations

AA: arachidonic acid
ACACA: acetyl-CoA carboxylase alpha
ACACB: acetyl-CoA carboxylase beta
ACAT: acetyl-CoA acetyltransferase
ACLY: ATP-citrate lyase
ACSL3/4: acyl-CoA synthetase long chain family member 3/4
ACSS2: acetyl-CoA synthetase 2
AGPAT: acylglycerophosphate acyltransferase (synonymous with LPAAT)
ALA: alpha-linolenic acid
AMPK: AMP-activated protein kinase
ccRCC; clear cell renal cell carcinoma
CPT1/2: carnitine palmitoyltransferase 1 and 2
CTLA-4: cytotoxic T lymphocyte-associated protein 4
CTSB: cathepsin B
DAG: diacylglycerol
DC: dendritic cell
DGAT: diacylglycerol acyltransferase
DHA: docosahexaenoic acid
EGFR: epidermal growth factor receptor
ELOVL: elongation of very long chain fatty acids protein
EPA: eicosapentaenoic acid
ER: endoplasmic reticulum
FA: fatty acid/s
FABP: fatty acid binding protein
FADS2: fatty acid desaturase 2
FAO: fatty acid oxidation
FASN: fatty acid synthase
FFA: free fatty acid/s
FSP1: ferroptosis suppressor protein 1
GLN: glutaminase
GLUD: glutamine dehydrogenase
GPAT: glycerol-3-phosphate acyltransferase
GPX4: glutathione peroxidase 4
HCC: hepatocellular carcinoma
HDL: high-density lipoprotein
HER2: human epithelial growth factor receptor 2
HIF-1α, -2α: hypoxia-inducible factor-1α, -2α
HMG: 3-hydroxy-3-methylglutaryl
HGMCR: HGM-CoA reductase
HMGCS: HMG-CoA synthetase
HSL: hormone-sensitive lipase
LA: linoleic acid
LCTH: mitochondrial long-chain 3-ketoacyl coenzyme A thiolase
LD: lipid droplet
LDL: low-density lipoprotein
LDLR: low-density lipoprotein receptor
LPA: lysophosphatidic acid
LPAAT: lysophosphatidic acid acyltransferase (synonymous with AGPAT)
LPC: lysophosphatidylcholine
LPCAT1: lysophosphatidylcholine acyltransferase 1
LPL: lipoprotein lipase
MDSC: myeloid derived suppressor cell
MITF: microphthalmia-associated transcription factor
mTOR: mammalian target of rapamycin
MUFA: mono-unsaturated fatty acid/s
MVK: mevalonate kinase
NK cell: natural killer cells
NSCLC: non-small cell lung cancer
PA: phosphatidic acid
PC: phosphatidylcholine
PD-1: programmed cell death protein 1
PDAC: pancreatic ductal adenocarcinoma
PDX: patient-derived xenograft
PE: phosphatidylethanolamine
PGC-1α: PPARγ co-activator-1α
PGE_2: prostaglandin E_2
PI: phosphatidylinositol
PIP4: phosphatidylinositol-4-phosphate
PLA: phospholipase
PLA2: phospholipase type A2
PPAR: peroxisome-proliferator activated receptor
PS: phosphatidylserine
PUFA: poly-unsaturated fatty acid/s
ROS: reactive oxygen species
SCD: stearoyl-CoA desaturase
SFA: saturated fatty acid/s
SLC7A11: Solute carrier family 7 member 11 (also known as xCT)
SQS: squalene synthase
SREBP-1, -2: sterol regulatory element binding protein-1, -2
TAG: triacylglycerol
TAM: tumor-associated macrophage
TCA cycle: tricarboxylic acid cycle
TCR: T cell receptor
T_{eff} cell: effector T cell
T_{ex} cell: exhausted T cell
Th1: T helper 1 cells
TME: tumor microenvironment
T_{mem} cell: memory T cell
TNBC: triple-negative breast cancer
Treg: regulatory T cell
VEGF: vascular endothelial growth factor
VLDL: very low-density lipoprotein

Declaration of Interest

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Figures

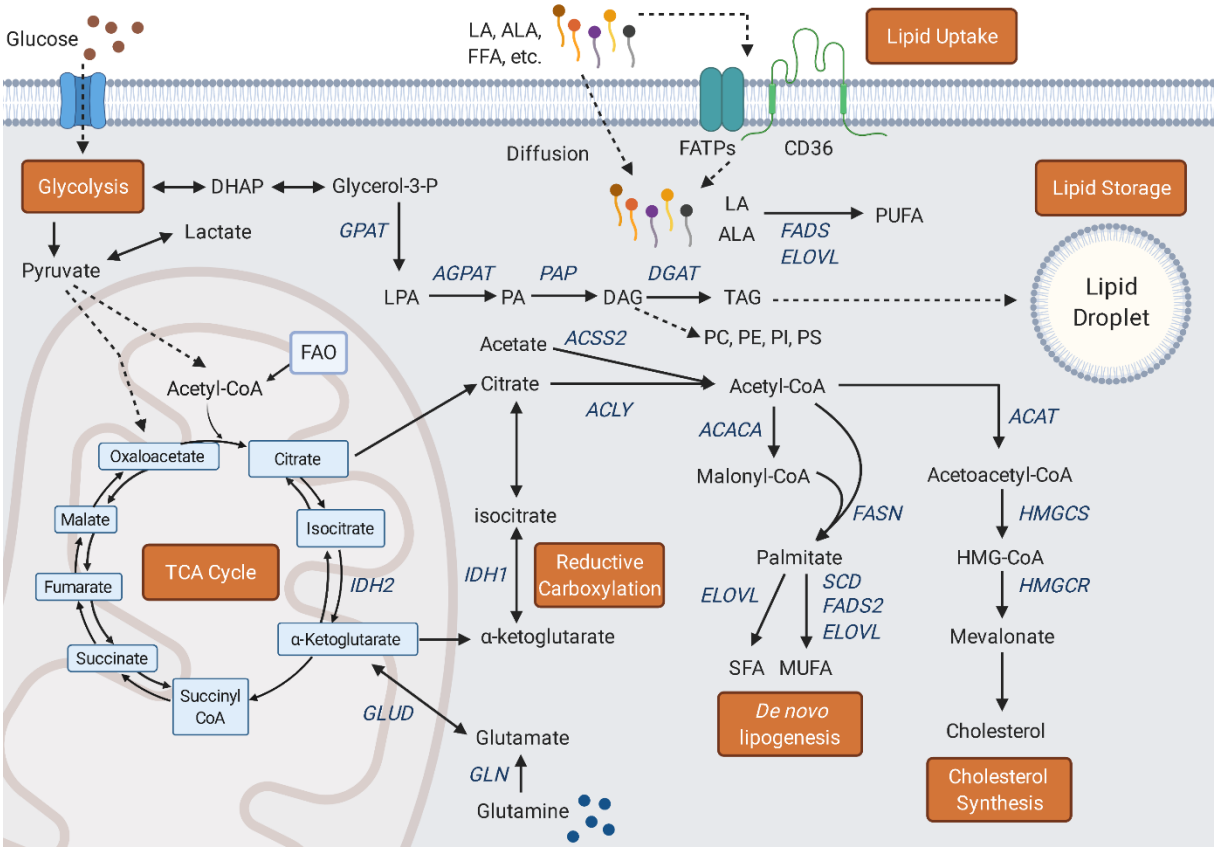

Figure 1: Major lipid metabolism pathways.

Cellular lipid metabolism is supported by all major macromolecules. Lipids can be brought into cells via passive diffusion and FA transport or translocase proteins, including FATPs and CD36. Glucose uptake and glycolysis provide pyruvate and acetyl-CoA to support cycling of the TCA cycle. Mitochondrial FAO is another source of acetyl-CoA in the mitochondria for TCA metabolism. Citrate is synthesized during TCA cycling, and is exported from the mitochondria as a first step towards *de novo* lipogenesis. Glutamate is another potential source of acetyl-CoA, where reductive carboxylation can support cytosolic citrate pools via α-ketoglutarate and isocitrate and the cytosolic and mitochondrial enzymes IDH1, and IDH2, respectively. Acetate can also be used to generate acetyl-CoA through ACSS2, also in the cytosol. Citrate is converted to acetyl-CoA by ACLY, providing the main 2-carbon building block for both FA synthesis and cholesterol synthesis. ACACA catalyzes the rate-limiting step in *de novo* lipogenesis producing malonyl-CoA. Acetyl-CoA and malonyl-CoA are used to produce palmitate, which can be further modified by ELOVL enzymes (to elongate the FA chains) and with the desaturases SCD and FADS2, generating SFA and MUFA. Furthermore, taken up essential FA (LA and ALA) can be turned into different PUFA through the action of FADS and ELOVL enzymes. Cholesterol synthesis utilizes acetyl-CoA to produce acetoacetyl-CoA by ACAT. HMGCS produces HMG-CoA, which is converted to mevalonate by HMGCR (the rate-limiting step in cholesterol synthesis), and further processed into cholesterol species. Lipids can be stored in LDs after they are combined into TAG species using glycerol-3-phosphate as a backbone. GPAT combines glycerol-3-phosphate with a long-chain FA to produce LPA, which is the rate-limiting step in TAG synthesis. LPA is converted to PA by AGPAT, and then to DAG by PAP. DGAT catalyzes the final step to produce TAG species, which can then be sequestered and stored in LDs, synthesized within the ER membrane. DAG can be also used in the synthesis of phospholipids for membranes, with predominant species including PC, PE, PI and PS. ACACA: acetyl-CoA carboxylase alpha; ACAT: acetyl-CoA acetyltransferase; ACLY: ATP-citrate lyase; ACSS2: acetyl-CoA synthetase 2; AGPAT: acylglycerophosphate acyltransferase; ALA: α-linolenic acid; DAG: diacylglycerol; DGAT: diglyceride acyltransferase; DHAP:

dihydroxyacetone phosphate; ELOVL: elongation of very long lipids protein; FADS: fatty acid desaturase; FAO: fatty acid oxidation; FASN: fatty acid synthase; FATPs: fatty acid transport proteins; FFA: free fatty acid/s; GLUD: glutamine dehydrogenase; GLN: glutaminase; GPAT: glycerol-3-phosphate acyltransferase; HMGCR: HMG-CoA reductase; HMGCS: HMG-CoA synthetase; LA: linoleic acid; LPA: lysophosphatidic acid; MUFA: mono-unsaturated fatty acid/s; PA: phosphatidic acid; PAP: phosphatidic acid phosphatase; PC: phosphatidylcholine; PE: phosphatidylethanolamine; PI: phosphatidylinositol; PS: phosphatidylserine; PUFA: poly-unsaturated fatty acid/s; SCD: stearoyl-CoA desaturase; SFA: saturated fatty acid; TAG: triacyl glycerol; TCA cycle: tricarboxylic acid cycle.

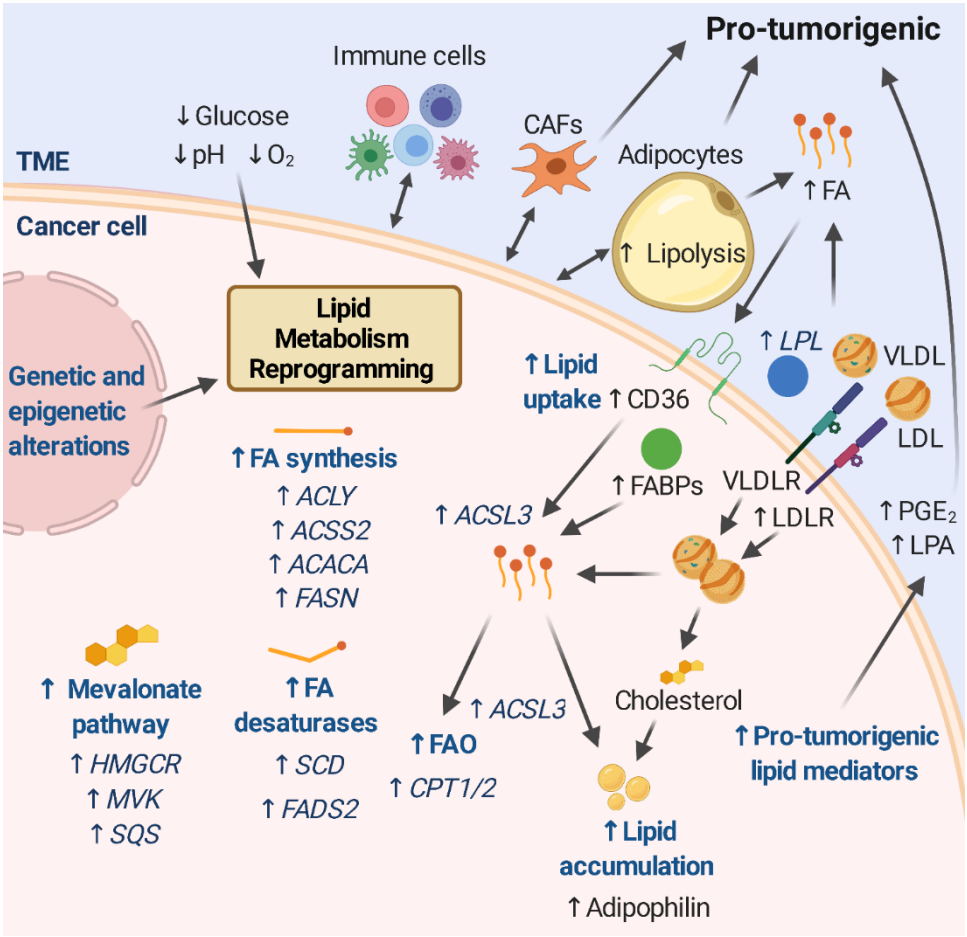

Figure 2: Cancer lipid metabolism reprogramming in the TME.

Tumor cells can dysregulate lipid metabolism for their own benefit, allowing them to adapt to adverse conditions. This reprogramming can originate from genetic and epigenetic alterations, and/or be driven by adverse conditions in the TME. An overview of the pathways that can be altered and examples of the upregulated proteins are depicted, as well as key actors in the TME with which tumor cells can interact. Some tumors can induce lipolysis in adjacent adipocytes, which release FA that can be taken up by cancer cells, supporting lipid accumulation and FAO. Lipoproteins can be also taken up by the tumor cells as a source of lipids. Different immune cells can exert anti-tumoral effects, but their functions are many times corrupted by the tumor, leading to immune-suppressive and even pro-tumorigenic states. The production of lipid mediators can also define tumor progression, for example promoting angiogenesis or affecting the immune compartment. Importantly, different tumors employ different adaptative mechanisms, which evidences the heterogeneity of lipid metabolism in cancer. ACACA: acetyl-CoA carboxylase 1; ACLY: ATP-citrate lyase; ACSL3: acyl-CoA synthetase long chain family member 3; ACSS2: acetyl-CoA synthetase 2; CAFs: cancer associated fibroblasts; CPT1/2: carnitine palmitoyltransferase 1 and 2; FA: fatty acids; FABPs: fatty acid binding proteins; FADS2: fatty acid

desaturase 2; FASN: fatty acid synthase; HMGCR: HMG-CoA reductase; LDL: low-density lipoprotein; LDLR: low-density lipoprotein receptor; LPA: lysophosphatidic acid; LPL: lipoprotein lipase; MVK: mevalonate kinase; PGE2: prostaglandin E_2; SCD: stearoyl-CoA desaturase; SQS: squalene synthase; VLDL: very low-density lipoprotein; VLDLR: very low-density lipoprotein receptor.

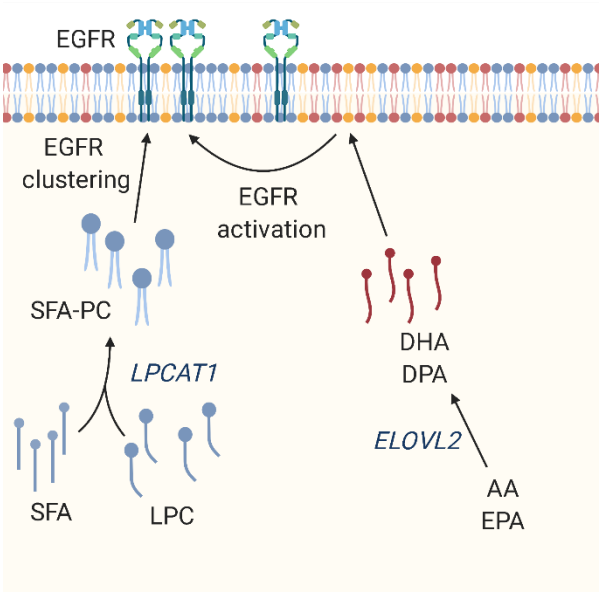

Figure 3: Membrane lipids may play roles in oncogenic signaling.

The composition of membrane phospholipids may play critical roles in modulating cell surface receptor signaling, for example by modulating EGFR clustering. LPCAT1 has a substrate preference for SFA, and by condensing a SFA and a LPC, it generates saturated PC, and this shift in the membrane lipid profile promotes EGFR clustering at the plasma membrane. ELOVL2 increases the incorporation of docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) into phospholipids by mediating the elongation of arachidonic acid (AA) or eicosapentaenoic acid (EPA). Similarly, these phospholipids are proposed to alter the plasma membrane in such a way as to promote EGFR activation. AA: arachidonic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; EGFR: epidermal growth factor receptor; ELOVL2: elongation of very long chain fatty acids protein 2; EPA: eicosapentaenoic acid; LPC: lysophosphatidylcholine; LPCAT1: lysophosphatidylcholine acyltransferase 1; PC: phosphatidylcholine; SFA: saturated fatty acid.

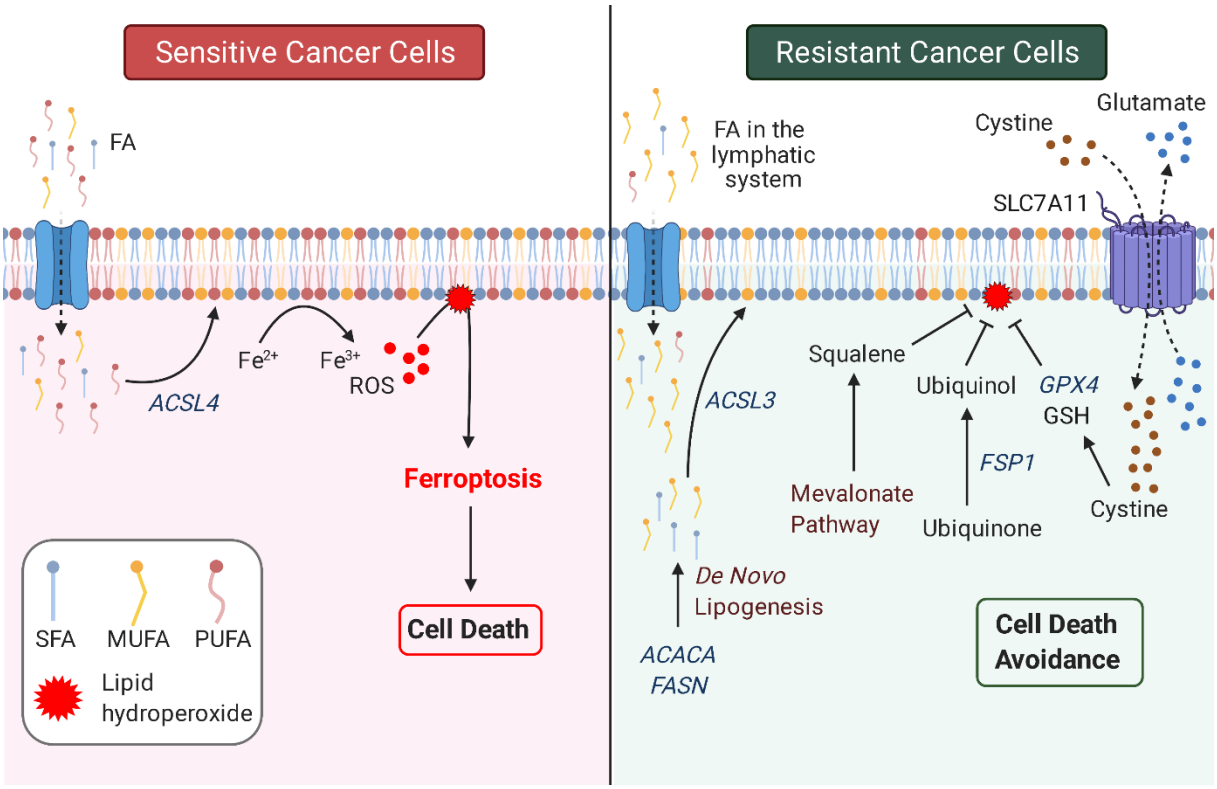

Figure 4: Lipid metabolism modulates ferroptosis susceptibility.

Ferroptosis is an iron dependent form of cell death that relies on the peroxidation of poly-unsaturated membrane phospholipids. Several lipid-based mechanisms can work in concert to either promote or reduce ferroptosis susceptibility. Increased lipid uptake can enrich cancer cell membranes in PUFA species and promote ferroptosis. In contrast to *de novo* synthesized FA, diet and stroma derived exogenous FA are generally more enriched in PUFA, especially since most normal tissues are low lipogenic. ACSL4 is an enzyme that is important in incorporating PUFA species into membrane lipids and can thereby render cells more ferroptosis sensitive. In contrast, certain environments such as lymph fluid are enriched in MUFA such as oleate. In this context, elevated exogenous lipid uptake enriches the membrane in MUFA and thereby renders the cell ferroptosis resistant in a process that is ACSL3 dependent. In contrast to ACSL4, ACSL3 is shown to be required for incorporating MUFA into membranes in some cancer models. Moreover, elevated lipogenesis which generates SFA and MUFA as end products, enriches membranes with phospholipid species that are ferroptosis resistant. In addition, the elevation of the cell's antioxidant potential is sufficient to inhibit ferroptosis. To this end, several mechanisms have been described, most notably, the roles of the cystine antiporter SLC7A11 in driving GSH synthesis and the GSH dependent membrane phospholipid hydroperoxidase GPX4. In parallel, additional critical GSH independent antioxidant mechanisms are known. These include the FSP1 dependent generation of the potent antioxidant ubiquinol and the generation of the radical-scavenging hydrocarbon squalene which is synthesized downstream of the mevalonate pathway. ACACA: acetyl-CoA carboxylase 1; ACSL3: acyl-CoA synthetase long chain family member 3; ACSL4: acyl-CoA synthetase long chain family member 4; FA: fatty acid/s; FASN: fatty acid synthase; FSP1: ferroptosis suppressor protein 1; GPX4: glutathione peroxidase 4; GSH: glutathione; MUFA: mono-unsaturated fatty acid/s; PUFA: poly-unsaturated fatty acid/s; ROS: reactive oxygen species; SFA: saturated fatty acid/s; SLC7A11: Solute carrier family 7 member 11 (also known as xCT).

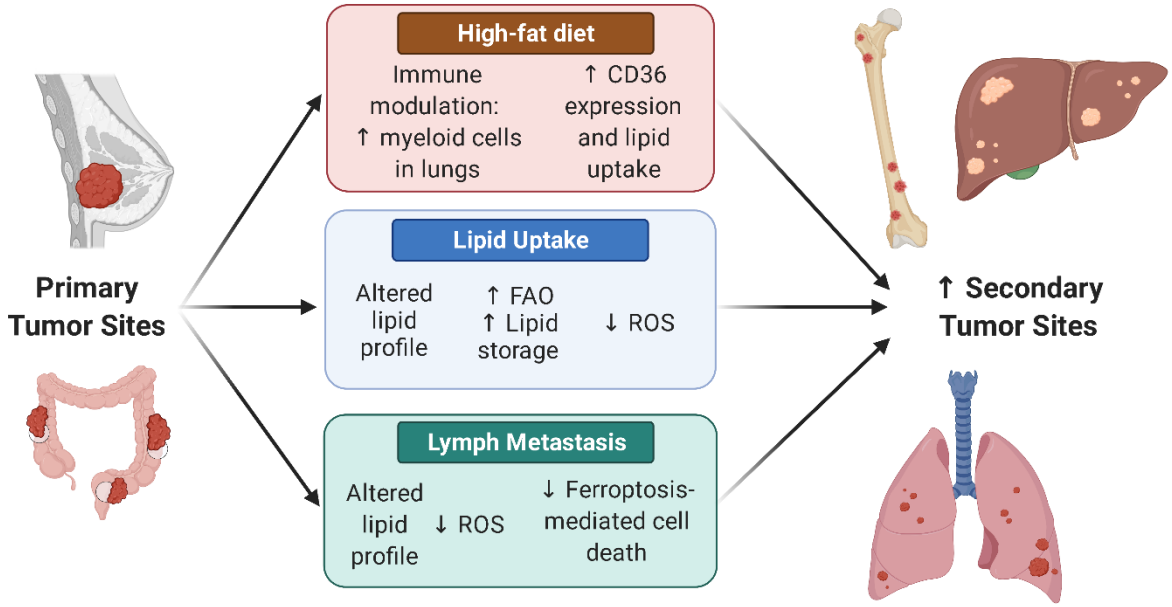

Figure 5: Lipid-related mechanisms supporting cancer metastases.

Lipid availability due to diet and in the TME can influence metastatic progression in a number of ways. Several pre-clinical models find that high-fat diet feeding increases secondary tumor sites in several mouse models, including breast and colon cancer primary tumors. Lipid availability may enhance metastases by providing lipid substrates for energy production and for biosynthetic processes supporting cell proliferation. High-fat diet feeding has also been shown to modulate the myeloid compartment in lungs, associated with increased lung metastases. Increased lipid uptake, in part driven by elevated CD36 expression, creates an altered lipid profile in metastatic tumor tissue compared to adjacent normal tissue, and primary tumor tissue. Metastatic tumors exhibit increased FAO, increased lipid storage in LDs, and subsequently decreased ROS production. When disseminated cells pass through the lymphatic system, which has been shown to be rich in oleic acid, their lymph metastases also express an altered lipid profile. Recently, lymph metastases have been shown to present decreased ROS production and ferroptotic cell death, in part due to increased oleic acid uptake. Overall, numerous mechanisms may be involved in lipid-mediated metastasis, supporting secondary tumor development in tissues such as the bone, liver and lung. FAO: fatty acid oxidation; ROS: reactive oxygen species.

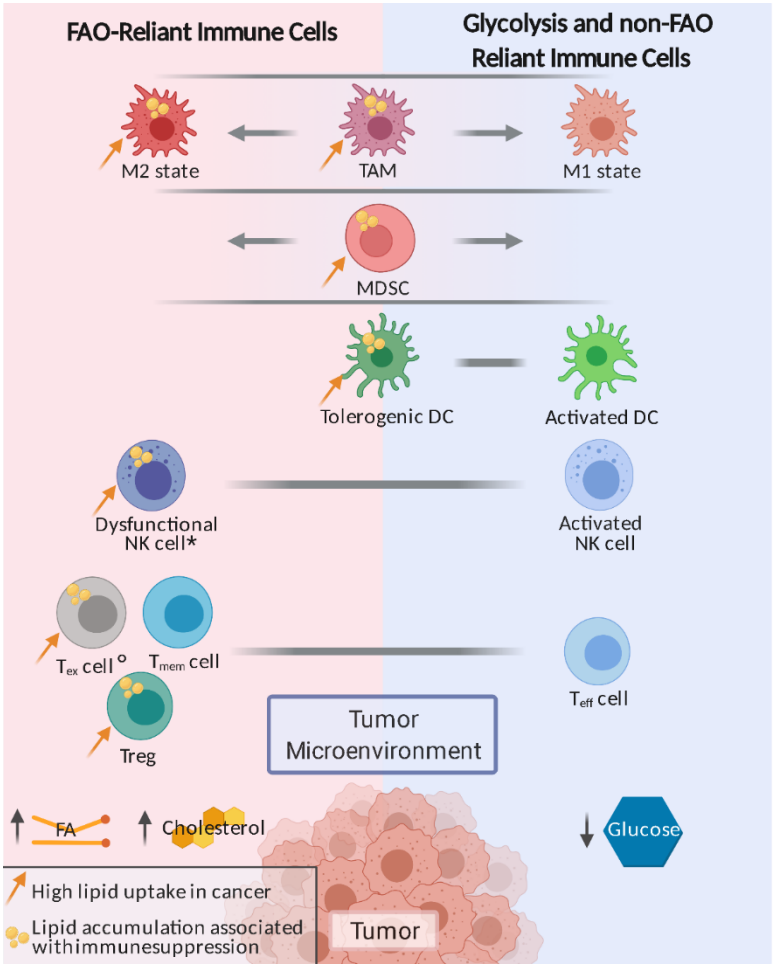

Figure 6: Immune cells' metabolic phenotypes in the TME.

Most tumor-associated immune cells show a metabolic program biased either towards glycolysis or FAO. MDSCs and TAMs can present a wide range of metabolic phenotypes as represented by the faded banners. The low glucose and high FA levels in the TME support metabolic programs that rely on lipids; and lipid accumulation in some immune cells was associated with pro-tumorigenic and immune-suppressive phenotypes. DC: dendritic cell; FA: fatty acids; MDSC: myeloid derived suppressor cell; NK cell: natural killer cell; TAM: tumor-associated macrophage; T_{eff} cell: effector T cell; T_{ex} cell: exhausted T cell; T_{mem} cell: memory T cell; Treg: regulatory T cell. *Characteristics observed in the context of obesity and cancer (Michelet et al., 2018) and in the postoperative period of cancer (Niavarani et al., 2019). °Specific long-chain FA uptake and accumulation in dysfunctional $CD8^+$ T cells with an exhausted phenotype in pancreatic cancer (Manzo et al., 2020).

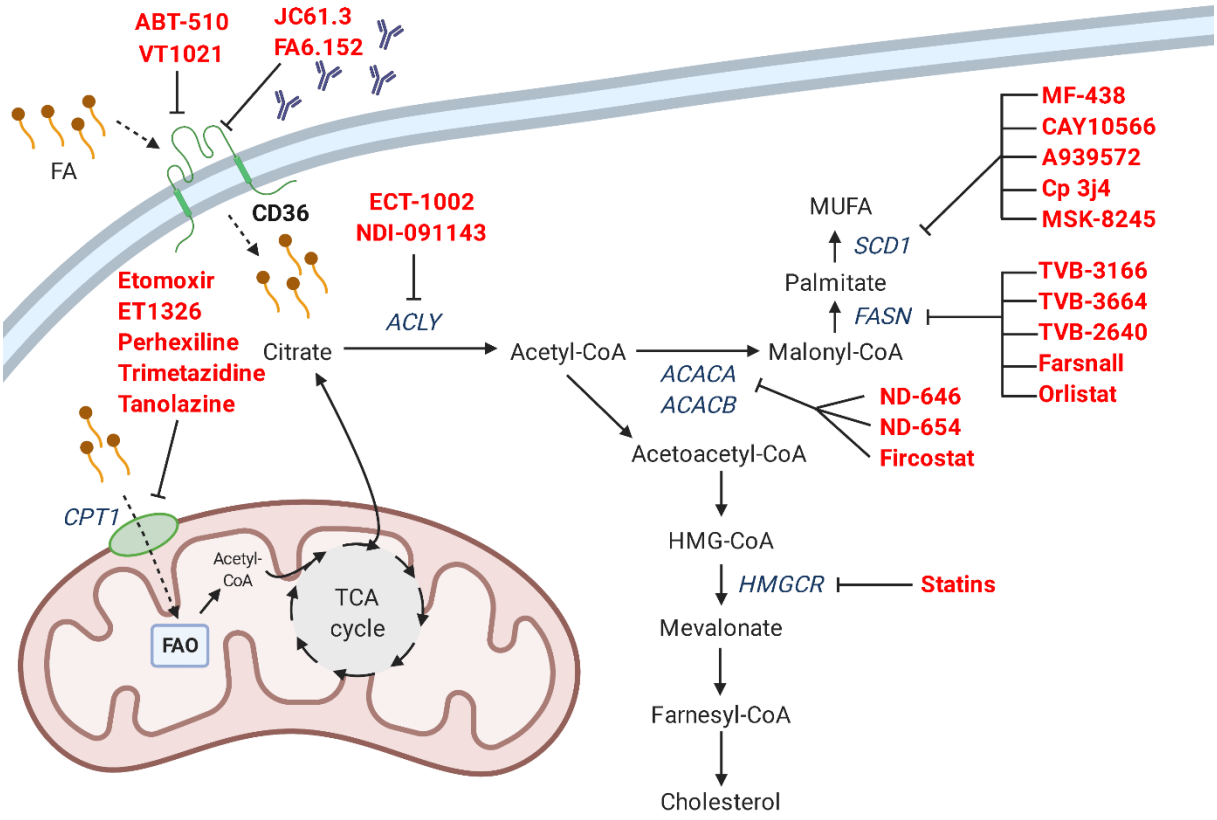

Figure 7: Inhibitors of lipid metabolism pathways.

Numerous drugs and small molecule inhibitors have been developed with the goal to inhibit cellular lipid metabolism, and provide opportunities for advancements in cancer therapies. FA uptake can be decreased by inhibition of the CD36 FA translocase by direct inhibitors (thrombospondin-1 analogues VT1021 and ABT-510), inhibitory antibodies (JC61.3, FA6.152). Preventing FA uptake into the mitochondria prevents mitochondrial FAO, and can impair cellular metabolism and citrate production for lipogenesis. There are a number of inhibitors of CPT1, the mitochondrial FA transporter, including etomoxir, ET1326, perhexiline, trimetazidine, and tanolazine. *De novo* lipogenesis can be inhibited at several points by pharmacological intervention. ACLY can be inhibited by ECT-1002 and NDI-091143, preventing acetyl-CoA production for the rate-limiting and irreversible carboxylation to malonyl-CoA by ACACA and ACACB. Direct inhibitors of ACACA/ACACB include the ND-646 and ND-654 compounds and fircostat. Malonyl-CoA is converted to the first FA generated by *de novo* lipogenesis, palmitate, by FASN. Several FASN inhibitors are available, including TVB compounds (TVB-3166, TVB-3664, TVB-2640, and farsnall). Further processing of palmitate can include conversion to MUFA and SCD1 catalyzes the rate limiting step, introducing a double bond into the carbon chain. This enzyme can be inhibited by several compounds (MF-483, CAY10566, A939572, Cp 3j4, MSK-8245). Statins are a class of drugs already clinically used for treating cardiovascular disease, and inhibit cholesterol synthesis at the rate liming step of HMGCR. ACACA: acetyl-CoA carboxylase alpha; ACLY: ATP-citrate lyase; CPT1: carnitine palmitoyltransferase 1; FA: fatty acids; FAO: fatty acid oxidation; FASN: fatty acid synthase; HMGCR: HMG-CoA reductase; SCD1: stearoyl-CoA desaturase 1; TCA cycle: tricarboxylic acid cycle.

Table 1 – Summary of small molecule inhibitors of lipogenic enzymes

Target	Compound	Mechanism	Tissue Distribution (and Bioavailability)	Pre-Clinical Evidence in Cancer	Clinical Trials (registered on clinicaltrials.gov)
ACACA/B	ND-646	Allosteric ACACA and ACACB inhibitor	Broad distribution	Inhibits NSCLC growth (xenografts and GEM model)(Svensson et al., 2016) Inhibits NSCLC cell line growth (Li et al., 2019; Svensson et al., 2016)	N/A
	ND-654	Allosteric ACACA and ACACB inhibitor	Liver-specific	Inhibits lipogenesis and carcinogen-induced HCC development, sensitizes against sorafenib (Lally et al., 2018)	N/A
	Firsocostat (previously: ND-630, GS-976)	Allosteric ACACA and ACACB inhibitor	Liver-specific	Inhibits lipogenesis in liver cancer cells (Harriman et al., 2016)	NASH (completed: NCT03449446, NCT02856555, NCT03987074; active: NCT02781584)(Alkhouri et al., 2020)
FASN	Orlistat	Covalently binds pancreatic lipase, irreversible binding of thioesterase domain of FASN(Flavin et al., 2010)	<1% orally bioavailable, lipophilic (Al-Suwailem et al., 2006)	Inhibits prostate xenograft growth, inhibits oral squamous cell carcinoma primary tumors and lymph metastases, enhances survival from gastric cancer, decreases melanoma lymph metastases (Agostini et al., 2014; Dowling et al., 2009; Kridel et al., 2004; Seguin et al., 2012) Inhibits prostate, colon, oral squamous cell carcinoma, melanoma, pancreatic, and breast cancer cell growth (Agostini et al., 2014; Chiurchiù et al., 2018; Kridel et al., 2004; Sokolowska et al., 2017)	N/A
	TVB-3166	Reversible FASN inhibitor	Orally bioavailable	Inhibits xenograft growth (pancreatic, ovarian cancers, NSCLC PDX), sensitizes with paclitaxel/docetaxel (Heuer et al., 2017; Ventura et al., 2015; Zaytseva et al., 2018) Inhibits lipogenesis and cell growth (colon, lung, breast, ovarian, pancreatic, prostate, hematopoietic cancers) (Heuer et al., 2017; Ventura et al., 2015; Zaytseva et al., 2018)	N/A
	TVB-3664	Reversible FASN inhibitor (TVB-3166 analogue)	Orally bioavailable	Inhibits colorectal PDX growth (Zaytseva et al., 2018)	N/A

				Inhibits lipogenesis and cell growth (colon, lung cancer cell lines)(Heuer et al., 2017; Zaytseva et al., 2018)	
	TVB-2640	Reversible FASN inhibitor	Orally bioavailable	N/A	NSCLC (NCT03808558) Solid tumors (Completed; NCT02223247) (Dean et al., 2016) Colon cancer (NCT02980029) $HER2^+$ Breast cancer (NCT03179904) Astrocytoma (NCT03032484) NASH (NCT03938246)
	Fasnall	Thiophenopyrimidine-based FASN inhibition	N/A	Inhibits breast cancer development and enhances survival (MMTV-Neu $HER2^+$ breast cancer), sensitized with carboplatin (Alwarawrah et al., 2016) Inhibits breast cancer cell growth and alters lipid profile (Alwarawrah et al., 2016)	N/A
ACLY	ETC-1002 (Bempedoic acid)	Active metabolite (ETC-1002-CoA) inhibits ACLY activity; allosteric AMPK inhibition	Orally bioavailable, pro-drug form activated in liver via acyl-CoA synthetase, suggesting liver-specificity (Bilen and Ballantyne, 2016; Pinkosky et al., 2016)	HepG2 liver cancer cell line unable to metabolize prodrug to active form but pro-drug form activates AMPK to inhibit lipogenic pathways (Pinkosky et al., 2013)	Hyperlipidemia and hypercholesterolemia (all currently registered clinical trials completed, published summary available) (Bilen and Ballantyne, 2016)
SCD1	MF-438	Thiazole-pyridazine derivative, inhibits SCD1	Orally bioavailable; potent liver SCD inhibition	Inhibits thyroid cancer xenografts, sensitizes renal cancer xenografts to mTOR inhibition (temsirolimus) (Von Roemeling et al., 2013, 2015) Inhibits cancer cell growth and stimulates apoptosis (breast, thyroid, renal cancers), sensitizes NSCLC and melanoma to BRAF/MEK inhibitors, ferroptosis sensitizer in ovarian cancer (Noto et al., 2017; Pisanu et al., 2017, 2018; Von Roemeling et al., 2013; Tesfay et al., 2019; Zhao et al., 2017)	N/A

	CAY10566	Inhibits saturated LCFA-CoA conversion to MUFA-CoA	N/A (orally and intranasally bioavailable) (Liu et al., 2007; Pinkham et al., 2019)	Inhibits glioblastoma xenografts, ovarian tumor initiation, and melanoma lung metastases (Li et al., 2017; Liu et al., 2018; Pinkham et al., 2019) Inhibits ovarian cancer spheroids, colorectal cancer, inhibits lung fibroblast stimulation of melanoma metastasis, glioblastoma stem-like cells (Chen et al., 2016; Liu et al., 2018; Pinkham et al., 2019; Tesfay et al., 2019)	N/A
	A939572	Nicotinamide derivative inhibiting SCD1	Orally bioavailable	Delayed colorectal cancer xenograft growth and sensitizes to ceramide biosynthesis inhibitor (L-cycloserine), inhibits ovarian cancer xenografts, inhibits primary melanoma tumors but stimulates metastatic melanoma (Chen et al., 2016; Tesfay et al., 2019; Vivas-García et al., 2020) Ferroptosis sensitizer in ovarian cancer, inhibits thyroid and bladder cancer cell growth (Piao et al., 2019; Von Roemeling et al., 2015; Tesfay et al., 2019)	N/A
	Cpd 3j	Inhibition of SCD based on structure-activity relationship studies	Accumulates in liver and adipose; orally bioavailable	Alters lipid profile in liver cancer (xenograft and carcinogen-induced) (Vriens et al., 2019) Identified insensitive (HUH7 liver, A549 lung), partially sensitive (H460 lung, DI145 prostate) and sensitive (MDA-MB-468 breast, T47D breast) cancer cell lines (Vriens et al., 2019)	N/A
	MK-8245	Inhibition of SCD based on structure-activity relationship studies	Liver specific	N/A	Type 2 diabetes (completed trial: NCT00972322)
CD36	VT1021	Thrombospondin analogue	N/A	Anti-tumor activity in ovarian, pancreatic, and breast cancers (Cieslewicz et al., 2019)	Solid tumors (NCT03364400)
	ABT-510	Thrombospondin analogue	N/A	N/A	Failed primary endpoint (PFS) in metastatic melanoma (Markovic et al., 2007)
	JC61.3	Anti-CD36 antibody	N/A	Inhibits oral metastases (Jiang et al., 2019; Pan et al., 2019; Pascual et al., 2017) Inhibits oral and gastric cancer cell growth, prevents lipid droplet formation and cancer cell progression (Corbet et	N/A

				al., 2020; Jiang et al., 2019; Pan et al., 2019; Pascual et al., 2017)	
	FA6.152	Anti-CD36 antibody	N/A	Inhibits oral cancer primary tumor and metastases (Pascual et al., 2017) Prevents lipid droplet formation and cancer cell progression (Corbet et al., 2020)	N/A
	SSO	Oleic acid analogue, specific, irreversible binding to CD36	Orally available, mechanism of action at cell membrane surface	Inhibits FA uptake and cell growth in colorectal cancer co-cultured with CAFs and ovarian cancer cells co-cultured with adipocytes, inhibits oleate uptake, proliferation and migration of cervical cancer cells (Gong et al., 2020; Ladanyi et al., 2018; Yang et al., 2018)	N/A
DGAT	A922500	DGAT1 inhibitor	Orally bioavailable	Decreased LD size and invasion capacity in cervical cancer cells (Corbet et al., 2020), inhibited TG formation in liver cancer cells (Qi et al., 2012)	N/A
	AZD3988	DGAT1-specific inhibitor	Orally bioavailable	Decreased TAG synthesis and sensitizes to palmitate-induced cell death in prostate cancer cells(Balaban et al., 2019)	N/A
	AZD7687	DGAT1-specific, reversible inhibitor	Orally bioavailable	N/A	Completed phase I trials for obesity and T2D, significant GI side effects limiting use (Denison et al., 2014) (NCT01217905)
	PF-06424439	DGAT2-specific inhibitor	Orally bioavailable	Reduces gastric cancer mesenteric metastasis (Li et al., 2020a) Prevents LD formation and drives apoptosis in gastric cancer cells ((Li et al., 2020a) sensitizes breast cancer cells to cisplatin and doxorubicin (Hernández-Corbacho and Obeid, 2019)	N/A
	JNJ-DGAT2-A JNJ-DGAT2-B	DGAT2-specific inhibitors (Qi et al., 2012)	N/A	Inhibited TG synthesis in liver cancer cells (Qi et al., 2012)	N/A
CPT1	Etomoxir	Irreversible CPT1 (liver and muscle isoforms) inhibitor; off-target effects (complex I inhibition and coenzyme A	N/A	Inhibits prostate cancer xenografts, inhibited MYC-high expressing TNBC and ovarian PDX growth, inhibited tumor growth associated with immune suppression and tumor MDSC infiltration, DC pre-treatment enhanced antitumor activity and sensitized to anti-PD-1 therapy	Clinical trial for congestive heart failure halted due to liver toxicity (Holubarsch et al., 2007)

		depletion at higher concentrations)		(Camarda et al., 2016; Hossain et al., 2015; Sawyer et al., 2020; Schlaepfer et al., 2014; Zhao et al., 2018) Inhibits proliferation of myeloma, leukemia cells, potentiated apoptotic effects of chemotherapies in breast, colorectal, and prostate cancer cells, reduces ovarian cancer cell viability (Hernlund et al., 2008; Li et al., 2017; Samudio et al., 2010; Sawyer et al., 2020; Schlaepfer et al., 2014; Tirado-Vélez et al., 2012)	
	ST1326	Non-cleavable analog of palmitoylcarnitine; reversible, competitive binding of CPT1 (liver isoform)	N/A	Prevented development of lymphoma (Pacilli et al., 2013) Inhibited FAO and growth of Burkitt's and leukemia cells, stimulated apoptosis in leukemia cells (Gugiatti et al., 2018; Pacilli et al., 2013; Ricciardi et al., 2015)	N/A
	Perhexiline	Competitive CPT1 inhibitor (higher efficacy in myocardial tissue than liver tissue)	Orally bioavailable; accumulates in tissues; high accumulation in myocardial tissue, crosses blood-brain barrier (Kant et al., 2020)	Inhibits orthotopic and subcutaneous glioblastoma tumor growth (Kant et al. 2020), inhibits breast cancer tumor growth (Kant et al., 2020; Ren et al., 2015) Inhibits glioblastoma cell growth (independent from FAO inhibition), increases lipid storage and inhibits proliferation in prostate cancer cells, inhibits breast cancer cell proliferation and HER3 expression (Itkonen et al., 2017; Kant et al., 2020; Ren et al., 2015)	Completed trials for heart failure (NCT00839228) and hypertrophic cardiomyopathy (NCT00500552), and terminated for cardiomyopathy due to lack of efficacy (NCT02862600); known toxicity in patients with CYP2D6 mutations (Ashrafian et al., 2007)
	Trimetazidine	Low potency against CPT1; Inhibits LCTH and FAO	Orally bioavailable, enters myocardial tissue	Stimulates myogenesis in mouse model of cancer cachexia, proposed exercise memetic in cancer cachexia (Gatta et al., 2017; Molinari et al., 2017)	Clinically available for angina, tinnitus and dizziness* Clinical trials recruiting to test in hepatocellular carcinoma (NCT03278444, NCT03274427) Under active clinical trials for myocardial injury with angina and T2D (NCT03715582), chronic liver failure (NCT03737448)

2

Table 1: Summary of Lipid Metabolism Small Molecule Inhibitors. Summary of various small molecule inhibitors and associated drugs (including alternative/previous names), their mechanism of action, and any known information on the tissue distribution and bioavailability, a summary of pre-clinical evidence in *in vivo* and *in vitro* models, and a summary of clinical findings or registered clinical trials (as indicated by the given NCT numbers). N/A indicates information that is not available.

Abbreviations: ACACA/B: acetyl-CoA carboxylase alpha/beta; ACLY: ATP-citrate lyase; AMPK: AMP activated protein kinase; CAFs: cancer-associated fibroblasts; CPT: carnitine palmitoyl transferase; DC: dendritic cell; DGAT: diacylglycerol acyltransferase; FA: fatty acids; FAO: fatty acid oxidation; FASN: fatty acid synthase; GEM: genetically engineered mouse model; GI: gastrointestinal; HCC: hepatocellular carcinoma; HER2: human epithelial growth factor receptor 2; LCFA: long-chain fatty acid; LCTH: mitochondrial long-chain 3-ketoacyl coenzyme A thiolase; LD: lipid droplet; MDSC: myeloid derived suppressor cell; MMTV: mouse mammary tumor virus; MUFA: monounsaturated fatty acid; NASH: non-alcoholic steatohepatitis; NSCLC: non-small cell lung cancer; PDX: patient-derived xenograft; PD-1: programmed cell death protein 1; PFS: progression-free survival; SCD: stearoyl-CoA desaturase; TAG: triacylglycerol; TG: triglycerides; TNBC: triple-negative breast cancer; T2D: type 2 diabetes. * Clinical availability may differ between countries.