Review

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Targeting Lipids Interactions With the Immune System, Inflammatory Response, Cardiovascular Outcomes, and Their Role in Tumorigenesis

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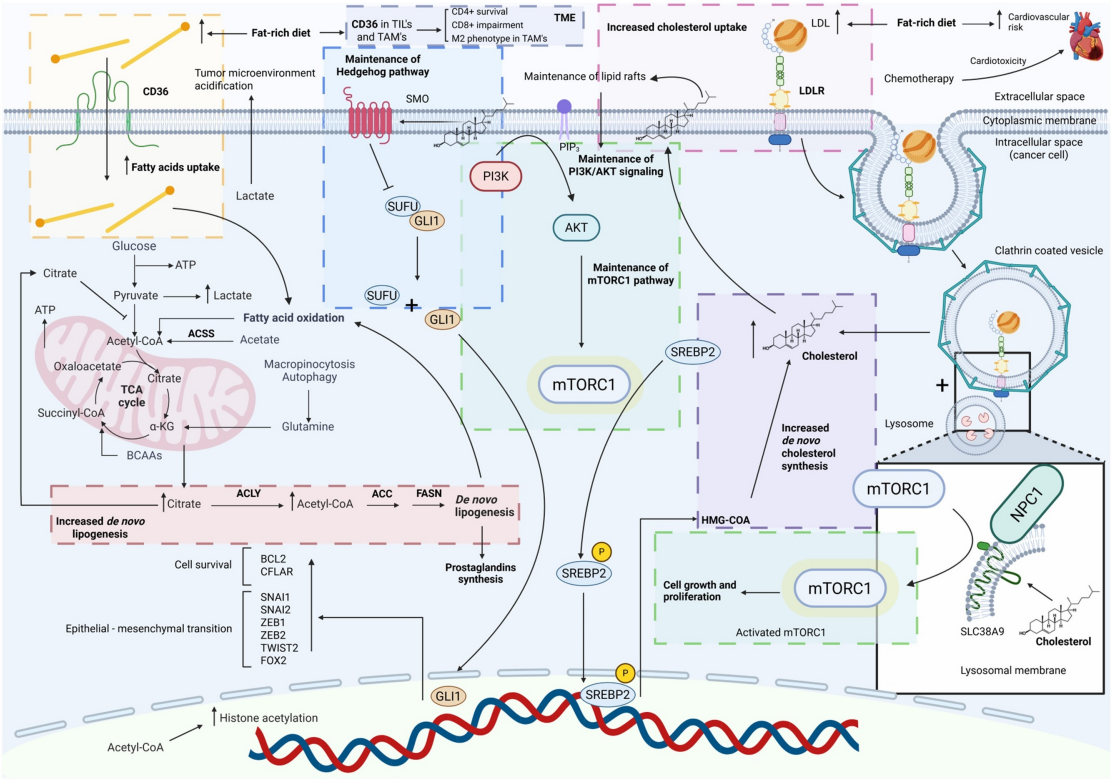
Lipids are a broad group of hydrophobic macromolecules that play critical roles in cell physiology, specifically in metabolism, membrane synthesis and signaling, which also includes the physiology of cancer cells. Due to the metabolic changes in cancer cells, lipids are used as an important energy source and signaling intermediates, which support the progression and survival of the transformed cells. Cholesterol is also an important part of these mechanisms, since it is an essential component of lipid rafts, which act as membrane platforms for signal transduction. Apart from the metabolism and signaling implication of lipids in cancer cells, these molecules may also affect histone modifications and the tumor microenvironment, modifying gene expression, cytokines secretion and the infiltration of white blood cells in the tumor, impeding tumor detections and clearance by the immune system. Due to the preponderant role of lipids in malignant cells, enzyme lipid uptake and synthesis represent potential therapeutic targets that are being studied to provide a complete treatment that focuses on different mechanisms to kill malignant cells. This review aims to provide a metabolic explanation about the influence of lipids in the survival of cancer cells, the immune response evasion, as well as some potential therapeutic targets that regulate these processes.

Keywords: lipid metabolism; cancer cells; lipid signaling; therapeutic targets; metabolic reprogramming



Graphical abstract of the main proteins involved in metabolic reprogramming in cancer cells. In bold: Upregulated proteins in several neoplasms and their effects on cell survival; Emphasizing: Fatty acids uptake, cholesterol uptake, de novo cholesterol synthesis, de novo lipogenesis, mTORC1 pathway, Hedgehog pathway. Glossary: ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; ACSS, acetyl-CoA synthetase; AKT, protein kinase B; FASN, fatty acid synthase; GLI1, glioma-associated oncogene homolog 1; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDL, lowdensity lipoprotein; LDLR, low-density lipoprotein receptor; mTORC1, mechanistic target of rapamycin complex 1; NPC1, NiemannPick C1 protein; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; SLC38A9, solute carrier family 38 member 9; SMO, smoothened receptor; SREBP2, sterol regulatory element-binding protein 2; SUFU, suppressor of fused homolog; TAMs, tumor-associated macrophages; TILs, tumor-infiltrating lymphocytes; TME, tumor microenvironment. Created in BioRender (https://www.biorender.com/).

Graphical Abstract.

Introduction

Lipids are one of the most important macromolecules in the cells and play essential roles in metabolism and membrane biosynthesis. However, in cancer cells, altered metabolism is a well-established hallmark [1], in which lipids play an essential role by providing an alternative pathway to fuel the energetic needs to sustain uncontrolled proliferation, cell growth, and division, as well as the synthesis signaling intermediates, membrane components, immune regulators and the modulation of epigenetic modifications [2]. These mechanisms are supported by evidence of an increased expression of lipid uptake transporters (such as cluster of differentiation 36 (CD36)) and enzymes required for the *de novo* lipid synthesis (ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), acetyl-CoA synthetase short-chain family member 1/2 (ACSS1/2), fatty acid synthase (FASN)) in malignant cells.

Evidence also suggests that targeting molecules that participate in the uptake, biosynthesis, and metabolism of lipids could be a useful therapeutic approach to treat cancer. As we will review in the upcoming sections, CD36 shows promise as a therapeutic strategy across several types of cancer, such as lung cancer, liver cancer, and myeloid leukemia, reducing lipid uptake by cancer cells and their viability. ACLY is also an interesting therapeutic target, since its inhibition, apart from the disruption of the metabolism of fatty acids (FA), also causes polyunsaturated fatty acid (PUFA) peroxidation, which damages the mitochondria and causes mitochondrial DNA leakage that activates the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) innate immune pathway.

Therefore, it is important to review lipids' many roles in the metabolism of cancer cells and elucidate potential therapeutic targets to provide a global treatment for neoplastic diseases (Table 1 provides a summary of the key proteins involved in lipid metabolism reprogramming and their therapeutic potential). This review comprehensively summarizes and discusses the available information regarding lipid uptake in cancer cells and in immune system cells within the tumor microenvironment (TME), including the crucial role of cholesterol in signal transduction. We also provide insights into the metabolic changes occurring in malignant cells, detailing the proteins and molecules involved in these processes. Furthermore, we explore the interrelationship between lipids and the immune system response, as well as the connection between lipids, tumorigenesis, and cardiovascular outcomes in cancer. Finally, this

Table 1. Key proteins in lipid metabolism reprogramming of cancer cells and their therapeutic potential.

Protein	Function	Effect on cancer cells	Therapeutic potential
CD36	Fatty acid transporter	• Increases lipid uptake, supports energy production, and promotes metastasis. • Enhances survival of Tregs in TME.	CD36 inhibitors reduce tumor growth and metastasis (e.g., in ovarian, liver cancer)
ACLY	Converts citrate to acetyl-CoA	• Fuels lipid synthesis and histone acetylation, promoting proliferation.	ACLY inhibitors (as SB-204990) disrupt lipogenesis and induce mitochondrial stress
FASN	Synthesizes palmitate	• Supports membrane biosynthesis, signaling, and chemoresistance. Overexpressed in aggressive cancers.	FASN inhibitors (e.g., TVB-2640) impair tumor growth and synergize with chemotherapy
ACC	Converts acetyl-CoA to malonyl-CoA	• Regulates fatty acid synthesis and oxidation. • Promotes survival under metabolic stress.	ACC inhibition disrupts lipogenesis and sensitizes cells to therapy
ACSS2	Converts acetate to acetyl-CoA	• Provides acetyl-CoA for lipid synthesis and histone acetylation under hypoxia.	ACSS2 targeting reduces tumor growth in nutrient-poor conditions
HMG-CoA Reductase	Rate-limiting enzyme in cholesterol synthesis	• Elevates cholesterol for lipid rafts and oncogenic signaling (e.g., Hedgehog).	Statins (e.g., atorvastatin) block cholesterol synthesis and show anti-cancer effects
SREBP1/2	Transcription factors for lipid synthesis genes	• Drives overexpression of lipogenic enzymes (FASN, ACC, HMGCR).	Dietary interventions show regulating effects in the expression of this protein

Glossary: ACC, Acetyl-CoA carboxylase; ACLY, Acetyl-CoA lyase; ACSS2, Acetyl-CoA synthase 2; FASN, Fatty acid synthetase; HMG, 3-hydroxy-3-methylglutaryl; SREBP, Sterol regulatory element-binding protein; TME, tumor microenvironment; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase.

review highlights some of the latest therapeutic proposals targeting lipid uptake and metabolism, while also emphasizing the critical need to consider their potential adverse effects.

Lipid Uptake

In tumors, several steps of lipid metabolism are upregulated to sustain cell proliferation; this includes an increase in lipid uptake, biosynthesis, storage, and fatty acid oxidation (FAO). The increase in the lipid requirement in cancer cells may be related to the need to synthesize membrane components. However, new mechanisms related to the function of lipids to promote the growth of cancer cells have been identified [2,3]. *De novo* lipogenesis (DNL) is a common process in cells that takes place mainly in adipocytes and hepatocytes. However, some lipids cannot be synthesized *de novo* and must be consumed in the diet and transported into the organs and cells. In the local microenvironment, cells internalize lipids primarily through the uptake of lipoproteins such as low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). These lipoproteins bind to specific cell receptors, like the low-density lipoprotein receptor (LDLR), which then mediate their entry into the cell via endocytosis [4,5].

CD36

CD36, also known as fatty acid translocase (FAT), fatty acid transport protein family (FATPs), and plasma membrane fatty acid binding protein (FABPpm), is an 88 kD glycosylated class B scavenger receptor expressed on the surface of dendritic cells, monocytes, macrophages and some subsets of B and T cells, as well as non-immune cells, such as immature erythrocytes, platelets, myocytes, adipocytes and specialized epithelial cells [6].

This protein binds to several ligands that can be grouped into three categories as follows: (1) proteins containing thrombospondin structural homology repeat (TSR) domains, (2) long-chain fatty acids (LCFAs), and (3) pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [6,7].

CD36 has two short transmembrane domains, which do not have intrinsic enzymatic activity, binding sites for GTPases to transmit signals, or scaffolding domains. However, CD36 triggers several intracellular signaling cascades [8,9]. Therefore, this protein must assemble a signalosome complex that includes intracellular and membrane proteins, such as toll-like receptors (TLRs) 2, 4, and 6, Na/K/ATPase, β 1/2 Integrins, and tetraspanins [9–13].

CD36-Mediated Lipid Uptake

This receptor's unique feature, which differentiates it from other pattern recognition receptors (PRRs), is its ability to facilitate LCFA transport in muscle, endothelial, and immune system cells such as macrophages and T cells [14–18]; this is an important feature in T cells, since the increase in the fatty acids uptake facilitates the survival of intratumoral regulatory T cells (Tregs), providing the demands for metabolic adaptation in the harsh TME [18]. An important characteristic of this LCFA transport is the subsequent in-

tracellular signaling that modifies the metabolism of lipids, which includes the upregulation of FAO by the signaling from the liver kinase B1, which activates the AMP-activated protein kinase (AMPK) pathway. Furthermore, the CD36/oxidized low-density lipoprotein (oxLDL) modulates the binding, uptake and intracellular cholesterol level, which has been studied in macrophages, showing that in the TME, the metastasis-associated macrophages (MAMs) and bone marrow-derived macrophages (BMDMs) show increased levels of triglycerides and diglycerides, as well as higher capacity to uptake LCFAs in comparison with their regular counterparts, which helps them to survive and proliferate in the harsh conditions of the TME [19].

CD36 has also been described as a protumoral factor in ovarian cancer (OvCa). As metabolic analysis suggests, CD36 generates the OvCa bioenergetic adaptation by creating a microenvironment rich in adipocytes that promotes metabolic plasticity. Also, like muscle cells, the expression of CD36 and subsequent fatty acid uptake can activate AMPK in a CD36-dependent and independent pathway. The silencing of the CD36 by short hairpin RNA (shRNA) showed a reduction in tumor size and metastatic capacity, positioning the CD36 targeting as a promising therapeutic strategy in different types of cancer [20].

Beyond its role in cell adaptation, CD36 activity in the TME creates a metabolic niche that promotes immune evasion and tumoral progression. For example, it has been shown that intratumoral Treg cells overexpress genes related to lipid metabolism and uptake, such as CD36, which allows the cells to survive in the TME, favoring immunosuppressive effects over tumor-infiltrating CD8+ T lymphocytes (tumor-infiltrating lymphocytes (TILs)) [18]. In addition to the immunosuppressive action by Tregs, TILs respond to the TME lipid concentrations by increasing CD36 expression, which leads to the accumulation of intracellular lipids that cause cell dysfunction and lipid peroxidation; the expression of CD36 in TILs has also been correlated with an exhausted phenotype of CD8+ T cells, which show diminished cytotoxicity. Another relevant finding in this context shows that oxidized LDL (OxLDL), which is abundant in the TME, suppressed the production of tumor necrosis factor (TNF) and interferon gamma (IFNγ) in CD8+ T cells *in vitro* in a dose-dependent manner [21]. This interaction is reversed when p38 is inhibited [22]. The intracellular OxLDL also induces lipid peroxidation, which is a form of oxidative stress that can activate p38 kinase and its downstream signaling pathways that induce death in CD8+ T cells, but not in CD4+ T cells, impairing the cytotoxic activity and favoring an immunosuppressive profile [23,24].

CD36 has also been identified as overexpressed in tumor-associated macrophages (TAMs), where it drives the intracellular accumulation of lipids that induce a metabolic reprogramming by promoting FAO and mitochondrial oxidative phosphorylation (OXPHOS) [6,25,26]. This enhanced lipid uptake not only supplies energy but also induces reactive oxygen species (ROS) production, that serve as signals to activate downstream pathways such as signal transducer and activator of transcription 6 (STAT6) phosphorylation, promoting an immunosuppressive M2-like phenotype [25]; in addition to this, CD36 also mediates the internalization of lipid rich extracellular vesicles and apoptotic cell-derived microRNAs (as miR-375), that further enhance TAM recruitment, migration and polarization toward an M2 phenotype that suppresses antitumoral responses [19,27].

In dendritic cells (DCs), CD36 expression leads to an excessive lipid accumulation that impairs antigen presentation by a decreased surface expression of the major histocompatibility complex (MHC) molecules, which reduces the dendritic cells' ability to stimulate T cells, resulting in compromised priming of antitumor responses [28]. Although some reports indicate that modest lipid accumulation may enhance pro-inflammatory cytokine secretion and improve cross-presentation—thereby stimulating natural killer (NK), natural killer T (NKT), and cytotoxic T lymphocytes [29], the excess, especially of oxidized or saturated fatty acids, typically skews DCs toward an immunosuppressive phenotype [30,31].

NK cells are similarly affected by the lipids in the TME. Their effector functions (tumor cell recognition, cytotoxic granule exocytosis, and cytokine production) rely on intricate metabolic reprogramming from glycolysis to oxidative phosphorylation. In the context of a TME loaded with fatty acids and cholesterol derivatives, NK cells accumulate intracellular lipids, which disrupts membrane integrity and impairs signaling at the immunological synapse [31,32]. Enhanced lipid uptake mediated by receptors like CD36 and subsequent activation of peroxisome proliferator-activated receptor (PPAR) pathways shift NK cell metabolism toward oxidative phosphorylation at the expense of glycolysis, leading to a state of metabolic paralysis. This metabolic shift results in reduced expression of key cytotoxic mediators such as granzyme B and perforin, thereby diminishing NK cell-mediated tumor killing [31,32].

Collectively, the altered lipid conditions in the TME create a metabolic obstacle that contributes to immune suppression. In DCs, excessive lipid accumulation impairs antigen presentation and T cell activation, while in NK cells, dysregulated lipid metabolism leads to reduced cytotoxic activity and interferon-γ production. Both cell types, therefore, experience functional dampening that facilitates tumor immune evasion. Therapeutic strategies targeting lipid uptake, metabolism, and storage (such as inhibition of fatty acid oxidation or modulation of cholesterol esterification) represent promising avenues to restore immune cell function and enhance antitumor immunity.

Lipoprotein-Mediated Lipid Transport: Cholesterol Role in Cancer

Low-density lipoprotein (LDL) distributes cholesterol throughout the extrahepatic tissues and cells of the body. This lipoprotein binds to the LDL receptor (LDLR) present in most tissues, which facilitates the LDL uptake by clathrin-mediated endocytosis. Once LDL is endocytosed, it fuses with lysosomes that hydrolyze the protein to release cholesterol, fatty acids, and amino acids. When cellular cholesterol levels are low, a transcription factor known as the sterol regulatory element-binding protein 2 (SREBP2) is cleaved and transported into the nucleus, where it upregulates the expression of LDLR [33–35].

Cholesterol is an important component of the cell membrane. It can be related to membrane receptors, through which cholesterol could directly activate oncogenic signaling pathways, such as the Hedgehog pathway, controlled by a G-protein–coupled receptor (GPCR). Reports indicate that cholesterol activates the oncogenic Hedgehog pathway by directly binding to the Smoothened receptor [36,37]. Additionally, cholesterol can bind the PSD95-Dlg1-ZO-1 (PDZ) domains of scaffold proteins, such as the N-terminal PDZ domain of Na^+/H^+ exchanger regulatory factor 1 (NHERF1, also known as ERM-binding phosphoprotein 50, EBP50), which is an important regulator of oncogenic signaling networks by the assembly of cancer-related proteins, like membrane receptors and signaling proteins involved in the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and Wnt/β-catenin pathways, that are related to cell proliferation and tumor formation [38–41].

Apart from its activities in the cell membrane, recent studies have also shown that lysosomal cholesterol has the ability to activate mechanistic target of rapamycin complex 1 (mTORC1) via the solute carrier family 38 member 9 (SLC38A9)—Niemann-Pick C1 signaling complex, leading to an increase in cell proliferation, invasion, and metastasis [42,43].

Cholesterol as a Component of Lipid Rafts

Lipid rafts (LR) are small lipid domains within the cell membrane constituted by cholesterol and sphingolipids. The lipid rafts work as platforms for signal transduction, and their structure and function can vary depending on the amount of cholesterol and phospholipids within the structure [44]. Changes in membrane cholesterol and components may be related to cancer progression and invasiveness [45,46]. For example, previous studies have shown that inhibition of cholesterol by methyl-β-cyclodextrin (MβCD) disrupts lipid rafts, inhibiting the AKT phosphorylation, which enhances apoptosis in cancer cells [47]. Another example is the hepatocyte growth factor receptor (c-Met) and the proto-oncogene tyrosine-protein kinase Src (c-Src) proteins, activated by phosphorylation and related to tumor formation and cell migration [48–50]. MβCD and lovastatin inhibit the aggregation and expression of these proteins, indicating that cholesterol depletion in LRs could inhibit the phosphorylation of lipid raft-associated Src and its subsequent pathway in lung cancer cell models [51,52].

Metabolism

In cancer cells, apart from the increase in lipid uptake, there is also an increase in DNL to support the elevated metabolic requirements. This pathway initiator is acetyl-CoA (AcCoA), mainly generated from citrate by the ATP citrate lyase (ACLY) in the tricarboxylic acid (TCA) cycle and by acetate conversion via acetyl-CoA synthetases (ACSS). Furthermore, ACC activates AcCoA to form malonyl-CoA, which is subsequently catalyzed by FASN to form SFA that can be further elongated and desaturated to synthesize monounsaturated fatty acids (MUFA) such as oleic acid and palmitoleic acid, and PUFA. The further desaturation of dietary PUFAs can produce other PUFAs like arachidonic acid, which is an important precursor to the synthesis of prostaglandins through cyclooxygenase (COX) and leukotrienes through lipoxygenase (LOX), that mediate several biological processes in the cancer context, including cell division, migration and differentiation [2,46].

ATP Citrate Lyase (ACLY)

The ACLY catalyzes the Mg-Mg-ATP-dependent transformation of citrate and CoA into oxalacetate (OOA) and AcCoA. Human ACLY is a 480 kDa tetramer composed of 4 identical subunits, each formed by the union of the N-N-terminal citryl-CoA synthetase (CCS) module and the catalytic C-C-terminal citryl-CoA lyase (CCL) domain. Elucidation of the enzyme structure has allowed researchers to design allosteric inhibitors that impede the citrate binding and enzymatic activity.

The ACLY plays a crucial role in cellular metabolism since it associates glucose metabolism with lipid metabolism, allowing AcCoA to “exit” the mitochondria as citrate. When in the cytoplasm, the ACLY divides the citrate and uses it as a substrate to recreate AcCoA and OOA, which are important precursors in metabolic routes, since AcCoA can be carboxylated by acetyl-CoA carboxylase into malonyl-CoA, the initiating step in fatty acid synthesis. However, the metabolic reprogramming in cancer cells is well known, based on a marked predilection for aerobic glycolysis to obtain energy (known as the Warburg effect). Some citrate sources in cancer cells come from the TCA cycle, upregulated by the increased glucose uptake or by the increased fatty acid oxidation (FAO) and potentially by extracellular citrate uptake [53–56]. Since ACLY is the last enzyme involved in the glycolytic cascade, the first step in lipid metabolism can impair cell metabolism by targeting a downstream effector and an initiating factor in these two pathways [54–56].

ACLY blockage through genetic or pharmacological means has been shown to suppress tumor growth in xenograft tumor models, although the effects were only cytostatic. Additionally, silencing ACLY using small interfering RNAs triggers apoptosis and inhibits cancer cell growth by increasing mitochondrial ROS production, which is more notorious in cells that exhibit low basal ROS levels. Another example of ACLY as a protumoral protein is the role of the ubiquitin ligase CUL3, which, when expressed, promotes ACLY degradation, which diminishes lipid synthesis and cell proliferation in lung cancer cells and cell proliferation in lung cancer xenograft models. On the other hand, low levels of CUL3 are associated with ACLY overexpression and worse prognosis in human lung cancer.

However, recent research showed that inhibition of ACLY may not be the best option for every type of cancer since the inhibition in a murine liver cancer model favored the upregulation of immune checkpoint inhibitors, comprising the treatment with immunotherapy [57].

Acetyl-CoA Synthetases (ACSS)

The coenzyme A carrier supports acetate, the shortest-chain fatty acid and the basic precursor for all long-chain fatty acids and sterols. Acetyl-CoA (AcCoA) is an important metabolic intermediate used in energy production and macromolecule biosynthesis, which supports cell growth and proliferation. Acetyl-CoA is also involved in acetylation processes that regulate cellular activity; thus, maintaining cellular Acetyl-CoA levels is important for the regulation of multiple processes [58,59].

Acetyl-CoA is produced by glucose oxidation and different carbon sources, such as glutamine and fatty acids, in humans. However, in human brain cancers, glucose accounts for less than 50% of the carbon required for the cellular AcCoA levels, suggesting the role of an alternative source of carbon for AcCoA [47]. Some studies show that malignant cells avidly capture acetate as an alternative carbon source under stress conditions, such as hypoxia [59–63].

Once the role of alternative carbon sources in the metabolism of cancer cells is established, it is important to note the participation of different enzymes in these pathways. Acetyl-CoA synthetase (ACSS) and acetyl-CoA carboxylase (ACC), and FASN are some enzymes related to metabolic processes in cancer cells.

There are three described isoforms of human ACSS, named ACSS1, ACSS2, and ACSS3; the function of ACSS3 is poorly understood nowadays. However, it is well known that ACSS1 and 2 have Acetate as substrate, while propionate is the preferential substrate of ACSS3 [64,65]. The ACSS proteins are the only known mammalian enzymes able to catalyze the conversion of acetate into AcCoA. The ACSS1 and 2 differ in their tissue distribution and subcellular location [64], where the ACSS1 is a mitochondrial matrix protein mainly expressed in cardiac and skeletal muscle and brown adipose tissue. Contrarily, ACSS2 is a nuclear and cytoplasmic enzyme, mainly expressed in the liver, kidney, heart, brain, and testis [66].

Another main difference between these two isoforms is their function, where ACSS1 participates in acetate oxidation, while ACSS2 contributes to lipid biosynthesis and promotes protein acetylation through the generation of AcCoA. Due to the need to utilize acetate, the majority of the cells express ACSS2 under characteristic physiological conditions [67], such as hypoxia, injury, nutrient deficiency, immune activation, and other processes [67,68].

ACSS2 in Cancer Metabolism

The presence of ACSS2 in cell nuclei is important since it supports the production of AcCoA to perform the acetylation of histones and transcription factors [69]. This enzyme was found to be expressed in triple-negative breast cancer, glioblastoma, liver cancer, and cervical cancer and is associated with poor survival of cancer patients [70–72].

ACSS2 has dual properties; under normal conditions, it functions as an enzyme involved in lipogenesis, promoting the synthesis and storage of lipids. However, under noxious conditions, such as nutrient deprivation, stress, or injury, the enzyme induces FA oxidation [68,73]. ACSS2 expression is promoted under deficient cholesterol and FA concentrations, and it is inhibited by elevated levels of these macromolecules [74,75].

It is important to note that ACSS2 is generally associated with tumorigenesis and increased malignancy in different neoplasia, such as ovarian, breast, glioblastoma, melanoma, fibrosarcoma, multiple myeloma, brain, and prostate cancers under nutrient-deprived conditions [68,70,72], however, in liver cancer, the ACSS2 downregulation in liver cancer cells associates with increased tumor incidence *in vivo*, where patients with low ACSS2 expression showed worse prognosis due to reduced anabolism and increased glycolysis and hypoxia [76].

This apparent contradiction in information reveals the need to study this topic further to clarify the implications of ACSS2 in different types of malignancies.

Fatty Acid Synthase (FASN)

As stated before, an accelerated DNL process is characteristic of cancer cells that require energy and lipids to maintain a high proliferation rate. The enzyme FASN is overexpressed in many cancers and is essential for the augmented synthesis of fatty acids [77]. The FASN is a ubiquitous cytosolic enzyme that catalyzes the biosynthesis of palmitic acid (C16:0) using malonyl-CoA and acetyl-CoA as substrates, using nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH), H^+ as co-substrates. This enzyme comprises two monomers that can attach head-to-tail or head-to-head [78,79]. Each monomer has seven different enzymatic activities that work sequentially, and an acyl carrier protein (ACP) that carries the acyl group dur-

ing the elongation process. A thioesterase (TE) portion of FASN releases the final product by hydrolysis [80,81].

The overexpression of FASN has been identified in many types of cancer, such as breast cancer, colorectal, prostate, stomach, esophagus, lungs, pancreas, ovaries, liver, melanoma, glioma, and primary effusion lymphoma [82–93], usually presenting as a poor prognostic marker.

The FASN participates in the metabolic reprogramming of malignant cells, favoring DNL, and in the nucleotide metabolism in non-Hodgkin lymphoma, where FASN promotes the nucleotide biosynthesis required to support malignant proliferation [94].

This interrelation relies on the use of NADPH, H^+, required to synthesize palmitate, where FASN reduces the levels of the co-substrate, promoting the activity of 6-phosphogluconate dehydrogenase (PGDH) by using and reducing the levels of NADPH, H^+, its allosteric inhibitor. PGDH is the second enzyme of the pentose phosphate pathway that generates ribulose-5-phosphate and is then converted into ribose-5-phosphate by the keto-isomerase (non-oxidative branch); this indirectly increases DNA/RNA synthesis by the FASN [77,94]. FASN is also implicated in protein expression through the activation of mammalian target of rapamycin (mTOR) activity in HepG2 and HCT116 cells [77,95,96].

Acetyl-CoA Carboxylase (ACC)

The eukaryotic ACC contains several domains, including biotin carboxylase (BC), biotin-containing carboxyl carrier protein (BCCP), carboxyltransferase (CT), an interaction domain (BT), and a non-catalytic center domain (CD). The CD comprises four domains: an N-N-terminal CDN, the linking CDL, and the tandem C-C-terminal CDC1 and CDC2 [86]. This enzyme facilitates the conversion of AcCoA to malonyl-CoA by the BCCP-linked biotin moiety (consuming ATP); then, the resulting carboxybiotin is shuttled to the CT domain and the carboxyl group to the AcCoA. Human ACC1 is inactivated when phosphorylated by AMP-activated protein kinase (AMPK) and by cAMP-dependent protein kinase (PKA); further, malonyl-CoA and its derivative palmitoyl-CoA [97,98].

The major function of ACC1 in fatty acid metabolism has drawn attention to its potential implications in cancer cell metabolism. For instance, the tumor suppressor BRCA1 regulates ACC1 by its C-C-terminal tandem BCRT domain, preventing the dephosphorylation of ACC1 and inhibiting its activation. However, genetic changes in the BCRT domain could interfere with the binding of BRCA1, leading to elevated lipogenesis, a hallmark of cancer cells supporting tumor growth [97,99].

ACC1 is also related to the initiation and development of several malignancies, such as myeloid leukemia, breast cancer, liver cancer, lung cancer, colon cancer, head and neck squamous cell carcinoma (HNSCC), and other diseases [99–106].

Cholesterol Metabolism

Apart from the increased cholesterol uptake in cancer cells, there is also an increase in *de novo* cholesterol synthesis. Cholesterol is biosynthesized through the mevalonate pathway, synthesizing 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), mevalonic acid (MVA), and squalene. The primary rate-limiting enzyme in this process is the HMG-CoA reductase, a pharmacological target inhibiting cholesterol synthesis [107]. The HMG-CoA regulation occurs via posttranslational modifications such as acetylation, ubiquitination, and phosphorylation that lead to its inhibition or degradation; however, in cancer cells the overstimulation of PI3K/AKT signaling and p53-mediated signaling pathways upregulate SREBP2 activity [108–110], which enters the nucleus and binds to the sterol regulatory element (SRE), promoting HMG-CoA synthesis that causes an increase in cholesterol levels [111–113]. As seen in the uptake section, cholesterol levels are essential for maintaining the lipid rafts' signaling capacity and associated components.

Histone Acetylation and Gene Expression

The nucleosome comprises a histone octamer around which the DNA wraps around. Histones are globular proteins susceptible to temporary covalent modifications [114]. Histone acetylation significantly alters the chromatin conformation, generally increasing transcriptional activity [114,115]. One of the limiting factors of this process is the presence of nuclear AcCoA. However, the metabolic reprogramming in cancer cells allows them to obtain AcCoA from other sources, including fatty acids, glutamine, acetate, lactate, and glycogen [116]. The AcCoA required for the acetylation may be generated from acetate or citrate by the enzymatic activity of ACLY and ACSS as described above, allowing the acetylation of H3K9, H3K18, and H3K23 under hypoxia conditions, which promotes the expression of *FASN* and *ACC1*, which are genes involved in lipogenesis that activate the DNL, favoring the survival of cancer cells [59].

Lipid Signaling and Transcription Factors

Lipid-related signaling is a complex process that involves several proteins whose mutations may affect the lipid metabolism needed for the survival of cancer cells. One example is the presence of mutated p53, which, in normal conditions, binds the promoter region of SERBP-1, inhibiting its expression and downregulating the expression of essential enzymes that participate in lipogenesis, as ACLY and FASN [117]; p53 also suppresses the pentose phosphate pathway, subsequently decreasing NADPH production necessary for lipid synthesis. However, mutated p53 in breast cancer promotes the proliferation of malignant cells by upregulating cholesterol biosynthesis through enzymes in the mevalonate pathway [118]. Also, p53-

mutated tumors show increased expression of crucial genes required for FA synthesis, such as FASN, ELOVL, and SCD1 [119,120]. On the other hand, p53 transcription induces CPT1, which increases FAO, reducing intracellular lipid accumulation, affecting the availability of energetic sources in the cell [117,121–123].

Other components implicated in cancer cells' survival and proliferation are those involved in the PI3K/AKT/mTOR (PAM) and MAPK (Add FASN-mTOR interaction) pathways. The PAM signaling pathway is highly conserved in eukaryotic cells and promotes cell survival, growth, and cell cycle progression in response to stimuli [123]. Dysfunctions in any of these components may lead to cancer development, as well as resistance to therapy and progression of the disease [123–126]. Two essential proteins that participate in this pathway are PI3K and AKT. In cancer cells, the growth factor-mediated induction of Receptor Tyrosine Kinases (RTKs) or GPCRs triggers the phosphorylation and activation of PI3K, which interacts with phosphatidylinositol 4,5-bisphosphate (PIP2), producing phosphatidylinositol (3,4,5)-trisphosphate (PIP3) at the plasma membrane, which serves as a docking site at the membrane for active AKT that now can phosphorylate downstream effectors, such as mTOR, which regulates glucose uptake, and lipid synthesis by promoting the transcription of SREBP [127,128]. Also, AKT inhibits apoptosis by phosphorylating pro-apoptotic proteins like B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra-large (Bcl-x), and Bcl-2-associated X protein (Bax) [129]. This pathway and its components represent promising therapeutic targets [127].

Immune System

Influence of Metabolism in the TME and Immune Cell Infiltration

Apart from supporting tumor development, the metabolic "rewiring" modifies the TME by altering immune cells' recruitment, activation, and function. Tumor cells modify the TME by secreting signaling molecules and metabolites that modify the functions of immune system cells and cancer-associated fibroblasts (CAFs) in the TME [130]. The metabolic reprogramming also causes an increase in lipid uptake and accumulation, as well as FAO, which enhances the survival of malignant cells and tumor progression [131]. An upregulation in the expression of CD36 in intratumoral Treg cells occurs, explicitly provoked by the conditions produced by cancer cells, but not by hypoxia and acidity alone, which supports the metabolic need for the immunosuppressive cells [18].

Another example of the influence of the TME in immune system cells is the case of tumor-associated macrophages (TAMs) in liver cancer, where low levels of RIPK3 promoted the M2 phenotype of TAMs by enhancing FAO through the ROS—caspase1-PPAR pathway [132]. This evidence suggests the potential role of components of lipid metabolism as therapeutic targets.

As stated in the metabolism section, TME and cancer cells produce eicosanoids (PGs and LTs) [133], negatively affecting the recruitment of cytotoxic T cells to tumors and the effects of immunotherapy, showing that the use of COX-2 inhibitors (celecoxib) may increase the response to immunotherapy [134]. It is important to note that COX-2 overexpression is a phenotype shared by aggressive and metastatic potential in cancers of the colon, lungs, pharynx and larynx, pancreas, and breast [135–139]. In a lung cancer model, the increased PGE2 synthesis and the induction of an immunosuppressive phenotype in myeloid-derived suppressor cells (MDSCs) coexist [140]. Previous evidence showed that PGE2 collaborates with TGF-B and induces the expression of FOXP3 to increase the production of Tregs [141,142]. Additionally, PEG2 association occurs with the expression of immune checkpoint inhibitors, such as PDL1 [143,144].

Dendritic cells (DCs) and NKs are critical in combating cancer cells. However, PGE2 can impair their activity, affecting the NKs' viability and cytokine production and diminishing the recruitment of DCs to tumors. However, this mechanism is not fully elucidated [145].

The therapeutic targeting of PEG2 receptors may be a reasonable strategy, but four different receptors add complexity to this task. However, differently designed inhibitors target individual receptors. For example, antagonists against EP4 that require cAMP in their pathway have shown efficacy when combined with other therapies to reestablish the immune system's ability to fight cancer cells and stop cancer progression and invasion capacities [146,147]. Clinical studies are still in progress [148].

Lipids, Tumorigenesis, and Cardiovascular Outcomes in Cancer

Due to advances in technology, prevention, early detection, and more targeted treatments, the survival rate of patients diagnosed with cancer has increased, which has made possible the study of late effects of this disease and its therapy in a long-term health condition context [149].

Cardiovascular disease (CVD) is one of the foremost prevalent leading causes of death among cancer survivors, leading to thinking of common risk factors and pathophysiological mechanisms that predispose patients to both cancer and CVD [149]. In addition to this, the average age of oncology patients is also increasing with the aging of the population in general, which may have pre-existing CVD risk or risk factors for CVD [150].

A high incidence of CVD, including coronary heart disease (CHD), heart failure (HF), and stroke, has been identified among adult survivor patients. It is interesting to note that cancer survivors have a 37% higher risk of incident CVD and 52% higher risk of HF in comparison to individuals without prior cancer [149].

Multiple studies identified common risk factors, in which high blood pressure, diabetes, dyslipidemia, excess weight, smoking, and impaired immune response have been highlighted [149]. The idea of shared risk factors is also strengthened by the fact that 10-year risk scores for atherosclerotic CVD may also be predictive for cancer [151].

Obesity and the frequent intake of high-fat diets are related to the incidence and aggressiveness of specific cancers. Obesity is recognized as an independent risk factor for distant metastasis, therapeutic resistance, and mortality in various cancers. Evidence also suggests that early activation of lipid metabolism in non-cancerous tissues by high intake of fatty acids can promote tumor initiation [152]. Likewise, shared potential mechanisms such as systemic inflammation and oxidative stress, a pro-inflammatory and prothrombotic state promoted by cancer and its therapies, play an important role [149].

Emerging evidence suggests that metabolism plays a key role in CVD and cancer. Cardiomyocytes' catabolic demands rely predominantly on using fatty acids (FA) under normal physiological conditions. While in the context of HF, cardiac metabolism shifts to glycolytic ATP provision, creating a metabolic profile similar to tumor cells, where, as reviewed in previous sections, malignant cells modulate metabolic pathways to coordinate catabolic and anabolic activities to achieve the cellular homeostatic, energetic, and biosynthetic needs [151]. An example of oncogenic remodeling in proliferating cells is the Warburg effect, where glycolysis is preferred even in the presence of oxygen [153].

Excessive accumulation of lipids or a shift in saturated and unsaturated FA levels can disrupt homeostasis and enhance cellular stress, which reflects on FA metabolism being also relevant in the development of chronic diseases and malignancies as breast cancer [151,154]. Saturated fatty acids (SFA) correlate positively with total mortality, while plasma polyunsaturated fatty acids (PUFAs) are inversely associated with total CVD mortality. Circulating n-3 PUFAs are associated with lower total CVD and cancer mortality. In comparison, linoleic acid (LA) is associated with lower total and CVD mortality, and non-LA n-6 PUFAs are linked to higher total and cancer mortality [155].

Omega-3 PUFAs exert anti-inflammatory properties, whereas omega-6 PUFAs serve as substrates for the biosynthesis of pro-inflammatory molecules. Both inflammatory mechanisms are linked with tumor-promoting and anti-tumor activities, with some exceptions [152].

The beneficial properties of n-3 PUFAs stem from several mechanisms, including a reduction in blood triglycerides (TG), blood pressure, and heart rate. Furthermore, these FAs help alleviate inflammation through modulation of IL-6 or TNF-α, and improve endothelial function while reducing oxidative stress [155].

On the other hand, following the consumption of lipid-rich food, circulating lipid levels increase significantly. High-fat diet (HFD) remodels the lipid composition of the TME, enhancing tumor cell metabolism, and in parallel, reduces nutrient availability for CD8+ T cells, and suppresses CD4+ T helper cell activation through autophagy impairment. HFD-induced obesity also increases the amount of circulating myeloid-derived suppressor cells and their recruitment in the TME, promoting tumor growth and metastasis by the inhibition of tumor-reactive T cells, leading to immunotherapy resistance [152].

Furthermore, an inverse association between total protein intake and all-cause mortality is also noted, with plant protein associated with a diminished risk of all causes and CVD mortality. This negative association can be explained by the amino acids contained in plant proteins, as they can upregulate glucagon, which downregulates the biosynthesis of enzymes necessary for *de novo* lipogenesis and upregulates the low-density lipoprotein receptors [156].

Based on this, nutritional adjustments are potential interventions to target cancer cells and reduce the risk of CVD:

- Consumption of vegetable oils and seafood to improve plasma levels of PUFAs in order to prevent chronic diseases and premature death [155].
- Diets with a low glycemic index can attenuate lipid metabolic activity and limit tumor progression [151].
- Omega-3 polyunsaturated fatty acids lower TG concentrations by 30% from baseline levels. In addition, they also modify the expression of lipid metabolism-associated genes such as *SREBP1* and *PPAR-*α [152,157].
- Among dietary interventions, fasting exerts a profound impact on metabolic regulation, positively influencing cancer prevention and treatment in mice. However, no clinical data currently support intermittent fasting in cancer patients [151].

Other metabolic-modulating therapies include the use of statins, which effectively lower cholesterol levels. However, the impact of statins on cancer incidence remains inconclusive. Likewise, it has been shown that bariatric surgery has long-term preventive effects on incident CVD and cancer [151].

On the other hand, it is well known that some chemotherapies, such as anthracycline, HER2-targeted therapies. VEGF inhibitor treatments can induce CVD by direct cardiotoxicity, effects on the vasculature, and disruption in immune-cardiovascular homeostasis, leading to left ventricular dysfunction, HF, hypertension, arterial thrombosis, arrhythmias, and venous thromboembolism, which leads to the necessity to find therapeutic alternatives to avoid these adverse effects [150,151].

Thus, this data established that the connection between cancer and CVD surpasses conventional risk factors. Therefore, traditional risk assessment tools may often diminish the risk in these patients, meaning that risk factor adjustment by themselves is insufficient to fully undertake CVD risk in these patients [149].

This information provides healthcare professionals with a multidisciplinary approach about the importance of cardiovascular health before the initiation of oncological treatment and enables them to optimize the management of pre-existing CVD and modifiable cardiovascular and possible oncological risk factors [150].

Advances in Therapeutic Targets

Targeting Lipid Uptake

As described above, tumor cells have an increased lipid uptake to sustain biosynthesis and energetic needs, providing a potential therapeutic target. Targeting CD36 is a promising therapeutic strategy against different types of cancer, such as lung, liver, and myeloid leukemia, reducing lipid uptake by cancer cells and their viability [158–161].

Targeting Lipid Synthesis

Apart from the increased lipid uptake, cancer cells also exhibit increased DNL. Therefore, several strategies could complement the conventional treatment to eradicate cancer cells. ACLY expression in cancer cells is related to resistance to vemurafenib in a tumor-bearing mouse model. However, with the concomitant administration of SB-204990, vemurafenib showed a better suppressive effect on cancer cells [162].

Fatty Acid Synthetase (FASN)

As explained previously, the dysregulated lipid metabolism in cancer cells provides energy to sustain tumor progression. This altered metabolism enhances the metastatic potential of tumor cells and the development of chemotherapy resistance [95]. Therefore, several mechanisms to impair lipid metabolism have been tested, obtaining promising results. For instance, using FASN inhibitors showed the capacity to disrupt microtubules selectively in tumor cells and, combined with chemotherapeutic agents, significantly increases tumor growth inhibition in lung cancer cell lines [163]. Studies documenting the use of FASN inhibitors in clinical trials show improved therapy and general outcomes [164].

Also, targeting FABPS has shown promising antitumor effects in combination with conventional chemotherapy in mutant therapy-resistant prostate cancer cells [165].

ACLY is also an interesting therapeutic target since its inhibition, apart from disrupting the metabolism of FA, also causes PUFA peroxidation, which damages the mitochondria, and causes mitochondrial DNA leakage that activates the cGAS—STING innate immune pathway [57].

Lipid-Lowering Drugs

Bezafibrate

Over the years, the knowledge about the impact of lipid-regulating drugs in the context of cancer progression has increased. One of these groups is the bezafibrate drugs, which, by their mechanism of action as activators of the nuclear receptor PPAR-alpha, regulate the transcription of genes required for lipid metabolism and promote a much more regulated response by T cells in the TME. In addition, it enhances mitochondrial function in effector CD8+ T cells, promoting greater control of tumor growth. This drug was studied in preclinical models of mice with lung cancer, demonstrating a reduction of cancer risk with prolonged use, in addition to reducing the risk of cancer in patients with coronary disease [166].

It is known that tumor cells have a higher cholesterol level than non-cancerous cells; for example, in hormonal tumors like breast and prostate cancer, cholesterol induces progression and provides sexual hormones derived from cholesterol. When cholesterol accumulates in excess, it generates cholesteryl acyltransferase 1 (ACAT1) and cholesterol esters; a greater quantity of the latter promotes tumorigenesis. ACAT1 is overexpressed in glioblastoma and hepatocellular carcinoma; therefore, it could be a potential treatment target. In metastatic cancer, specifically prostatic, a higher concentration of lipids is related to greater progression and mortality; the administration of statins is associated with lowering the risk of metastasis by 49%, according to a 25-year follow-up study [167].

Statins

Statins are a group of drugs used for reducing levels of the novo cholesterol and modifying the low-density lipoprotein receptor; these drugs are currently being studied as cancer therapy and prevention. There is a difference between the hydrophilic and lipophilic statins, the latter being the best at penetrating the cells and having a higher apoptotic activity [167,168].

Cells acquire cholesterol via endocytosis or from the mevalonate pathway; this induces and promotes the YAP and TAZ protein activity; these proteins regulate tumor growth. The statins block the mevalonate pathway, blocking the formation of YAP and TAZ. Autophagy may play a role as one of the multiple mechanisms to target and limit cancerous cell growth by removing all damaged organelles. However, this can only happen in the early stages, as autophagy can promote tumorigenesis in more advanced stages. Statins can induce autophagy in healthy and cancerous cells with the regulation of AMPK (Activated Protein Kinase) and mTOR (Mammalian Target of Rapamycin) and AMPK/p21 (p21-activated kinase pathway) pathway and also with the accumulation of p53 caused by statins induce autophagy [167,169].

Statin therapy has also been tested in cancer cells, improving overall survival in patients with multiple myeloma, colorectal cancer, and pancreatic cancer when added to the first-line therapy [170–172]. It is also important to note that the concomitant use of these drugs with immune checkpoint inhibitors (ICI), has shown promising results, being related to an increased objective response rate in

one of the first studies that investigated the effects of concomitant drugs on the outcome on ICI therapy (PDL1) in patients with melanoma, kidney cancer and lung cancer (statin users vs non-users; HR: 1.6, 95% CI 1.14–2.25, $p = 0.0064$), although the use of statins didn't have effect on the progression-free survival nor overall survival [173]. However, more recent research also provided evidence about an increase of immune-related adverse events in patients treated with ICI therapy (PD1, PDL1, CTLA-4) and statins (OR: 1.199, CI: 1.141–1.261, FDR $p < 0.001$), showing both the benefits and risk of using concomitant drugs for cancer treatment, and the necessity to develop strategies to optimize the monitoring and prevention of adverse events in this context [174].

Lipid Metabolism-Modulating Agents

Another relevant group of drugs is ACAT1, HMGR, and SCD1 inhibitors. Their beneficial effects were investigated in patients with colorectal cancer in combination with treatment using 5-FU inhibitors, improving the therapeutic potential, reducing the doses of the chemotherapeutic drug during treatment, and showing growth-inhibiting effects on cancer cells. The drug of these groups that had a better response was avasimiba, showing synergy [175].

GSK126

GSK126 (a selective EZH2 enzyme inhibitor) inhibits histone methylation (H3K27me3), affecting the mTOR pathway that has an important role in cell growth and metabolism, including lipid synthesis. By inhibiting EZH2 and altering the epigenetic landscape, GSK126 can reprogram gene expression and signaling pathways that control how cancer cells synthesize, store, and utilize lipids. Lipid synthesis increases with treatment with this group of drugs, giving way to unsaturated fatty acids. The combination of this drug with Stearoyl-CoA Desaturase 1 (SCD1) reduces cancer cell proliferation by its lipogenic effect with the catalytic activity of reductive desaturation of stearoyl-CoA (an 18-carbon saturated fatty acid) to oleoyl-CoA (an 18-carbon monounsaturated fatty acid with a double bond at position 9) [176].

Another recently proposed alternative is the inhibition of CD36, which reduces lipid accumulation in cancer cells and is associated with inferior survival in breast cancer patients. Diets rich in fat promote CD36 expression and, thus, cancer metastasis. Palmitic acid induces gastric cancer cell migration through CD36 [168].

Sphingolipids

On the other hand, sphingolipids participate in tumorigenesis by increasing the resistance of malignant cells to drugs. Moreover, sphingolipids could be a promising biomarker measured by mass spectrometry techniques, which allows their identification in cancer cells, specifically ceramide, which plays an important role in necroptosis and autophagy. Targeted therapies based on sphingolipid signaling are currently being developed. Clinical trials indicate that sphingolipid-targeted therapies' efficacy and side effects vary, underscoring the need for a deeper understanding of their complex function.

Recent studies showed statins prolonged survival in patients with cancer in combination with their respective chemotherapy; there is a correlation between their use and a reduction of mortality in 13 different types of cancer; high doses of fluvastatin increased breast tumor apoptosis. Statins such as Atorvastatin and Rosuvastatin were associated with lower mortality and higher survival in metastatic cancer when administered with the corresponding chemotherapy. This drug has been studied for years; however, due to its promising results, studies continue to reveal the benefits of combining statins with chemotherapy [167,168].

Recent clinical trials are evaluating lipid metabolism targeting agents such as FASN inhibitors (e.g., TVB-2640) and ACLY inhibitors (e.g., bempedoic acid) for safety and efficacy in different kinds of cancers. For example, TVB-2640 has studies in Phase I in Solid Cancers [177,178] and has also advanced into Phase II trials for solid tumors such as Non-Small Cell Lung Carcinomas (NSCLC) [179]. Similarly, statins continued to be studied for repurposing in oncology, trying to test the benefits in Ovarian and breast cancer outcomes. Combining these metabolic interventions with immunotherapy is also under investigation, aiming to overcome immune resistance mediated by lipid metabolism in the tumor microenvironment [180,181].

Discussion

As reviewed, the metabolic reprogramming observed in cancer cells represents a hallmark of tumorigenesis, allowing these cells to survive and proliferate even in the harsh conditions of the TME [1]. An interesting debate within the field centers on whether this metabolic reprogramming primarily acts as a driver, initiating the malignant transformation of cells, or if it is predominantly a survival mechanism, allowing already transformed cancer cells to adapt and persist through metabolic rewiring [1]. Regardless, this adaptability is largely driven by altered lipid metabolism, which includes increased lipid uptake, *de novo* lipogenesis, and fatty acid oxidation, all of which provide essential energy and building blocks for rapid cell growth and division [3]. Key enzymes such as ACLY, ACC, ACSS, and FASN are frequently upregulated, fueling lipid synthesis and contributing to malignant cell survival [57,59–63,70–72,82,84,89,93]. Furthermore, cholesterol's pivotal role in the lipid rafts provides the platforms necessary for oncogenic signal transduction pathways, including the Hedgehog pathway and PI3K/AKT/mTOR, thereby directly promoting cancer cell proliferation and survival [38–41]. The intricate mechanisms behind this lipid reprogram-

ming underscore the necessity for continued in-depth research to fully comprehend the disease.

Beyond direct cell survival, dysregulated lipid metabolism significantly influences the immune system within the TME, contributing to immune evasion and shaping immune cell polarization. The TME's characteristics can modify the recruitment, activation, and function of various immune cells, where the increased expression of CD36 on intratumoral Tregs facilitates their survival in the TME, promoting immunosuppression and impairing the anti-tumor activity of cytotoxic TILs [23,24]. Similarly, TAMs overexpress CD36, leading to intracellular lipid accumulation and a metabolic reprogramming towards an immunosuppressive M2-like phenotype, which further suppresses anti-tumoral responses [19,27]. These mechanisms highlight the role of lipids in the generation of an immunosuppressive environment.

Another important area of investigation is the relationship between CVD, lipids, and cancer. With improved cancer survival rates, CVD has emerged as a leading cause of mortality among cancer survivors, pointing towards shared risk factors and pathophysiological mechanisms [149]. Common risk factors like dyslipidemia, obesity, and systemic inflammation contribute to the incidence and aggressiveness of both conditions, leading to the thinking of lipids as a link between these two entities. Therefore, dietary interventions have been proposed as an area of opportunity to enhance treatment response. Evidence indicates that high-fat diets can remodel the TME, favoring tumor growth and immunotherapy resistance [152]. These findings suggest that nutritional adjustments and dietary interventions, such as increasing PUFA intake and employing low-glycemic index diets, could be powerful strategies to impact both cancer progression and CVD risk [151,155].

The enhanced understanding of lipid metabolism in cancer allowed the identification and design of novel therapeutic strategies, offering promising interventions for patient recovery. Targeting lipid uptake via molecules like CD36 has shown potential in reducing tumor growth and viability in various cancers [158–161]. Similarly, inhibiting key enzymes in *de novo* lipogenesis, such as ACLY and FASN, has demonstrated the capacity to disrupt tumor metabolism, enhance sensitivity to chemotherapy, and impair metastatic potential [162–164]. Drugs like statins, primarily known for cholesterol lowering, are being repurposed due to their anti-cancer effects, including inducing apoptosis and improving survival in certain cancer types, especially when combined with conventional therapies [167,168,170–172]. Other emerging targets include ACAT1, HMGR, SCD1, and sphingolipid signaling. Clinical trials for FASN inhibitors (e.g., TVB-2640) and ACLY inhibitors (e.g., bempedoic acid) are currently evaluating their safety and efficacy [177–181].

However, as these novel therapeutic approaches emerge, it is imperative to recognize and thoroughly evaluate their potential adverse effects. Recent research has highlighted that the concomitant use of statins with immune checkpoint inhibitors (ICI) may increase the risk of immune-related adverse events, despite showing promising improvements in objective response rates in some patient cohorts [173,174]. These findings emphasize that while targeting lipid metabolism holds significant promise, a comprehensive understanding of potential side effects and the development of strategies for optimal monitoring and prevention are critical for ensuring patient safety and maximizing therapeutic benefit.

In summary, the intricate role of lipid metabolic reprogramming in supporting cancer cell survival, facilitating immune evasion, and influencing the complex interplay with cardiovascular disease highlights numerous avenues for therapeutic intervention. Further research is essential to fully clarify these mechanisms and to develop and refine targeted strategies that not only impair cancer progression but also consider and mitigate potential adverse effects, thereby leading the way for more holistic and effective patient management and potential therapeutic strategies targeting lipids while considering adverse effects.

Conclusions

Lipid metabolism plays a vital role in cancer biology; it supports tumor cell growth through energy production, membrane synthesis, signaling modulation, and survival by reprogramming the tumor microenvironment and evading immune surveillance. Cancer cells exploit the increased lipid uptake, enhancing *de novo* lipogenesis. Also, cholesterol metabolism adapts to metabolic stress, supporting cancer cell proliferation, facilitating metastasis, and, finally, resistance to therapy. Therefore, targeting crucial enzymes involved in the uptake, metabolism, synthesis, and transcription of proteins that regulate cell lipid roles is an adequate strategy to overcome the metabolic reprogramming in malignant cells.

Therapeutic strategies (including enzyme inhibitors, statins, bezafibrate, and dietary interventions) show promise in modulating lipid pathways and helping to improve oncologic and cardiovascular outcomes; however, adverse effects should be studied to further explore the safety of these novel treatments.

Finally, multidisciplinary cooperation is necessary to incorporate a holistic approach with oncologic, metabolic, and cardiovascular expertise, essential to developing personalized clinical care. Further research is needed in metabolism-based management to help with these individualized strategies and long-term outcomes.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, AHNZ, PMRA and SGS; writing – original draft preparation, PMRA, SGS, AVPP, KEOC, JAOF, BRJ and AHNZ; review framework production PMRA, JARC and SGS; writing – critical revision, PMRA, SGS, AVPP, KEOC, JAOF, BRJ, MGZC, JARC, ECV and AHNZ; graphical abstract, PMRA, MGZC and AHNZ; Investigation, SGS, PMRA, KEOC, AVPP, JAOF and ECV; visualization, BRJ, MGZC, ECV, JARC and AHNZ; supervision, BRJ, JARC, MGZC and AHNZ; project administration, SGS, BRJ and AHNZ. All authors have read and agreed to the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

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