Alterations of Lipid Metabolism in Cancer: Implications in Prognosis and Treatment

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Cancer remains the second leading cause of mortality worldwide. In the course of this multistage and multifactorial disease, a set of alterations takes place, with genetic and environmental factors modulating tumorigenesis and disease progression. Metabolic alterations of tumors are well-recognized and are considered as one of the hallmarks of cancer. Cancer cells adapt their metabolic competences in order to efficiently supply their novel demands of energy to sustain cell proliferation and metastasis. At present, there is a growing interest in understanding the metabolic switch that occurs during tumorigenesis. Together with the Warburg effect and the increased glutaminolysis, lipid metabolism has emerged as essential for tumor development and progression. Indeed, several investigations have demonstrated the consequences of lipid metabolism alterations in cell migration, invasion, and angiogenesis, three basic steps occurring during metastasis. In addition, obesity and associated metabolic alterations have been shown to augment the risk of cancer and to worsen its prognosis. Consequently, an extensive collection of tumorigenic steps has been shown to be modulated by lipid metabolism, not only affecting the growth of primary tumors, but also mediating progression and metastasis. Besides, key enzymes involved in lipid-metabolic pathways have been associated with cancer survival and have been proposed as prognosis biomarkers of cancer. In this review, we will analyze the impact of obesity and related tumor microenviroment alterations as modifiable risk factors in cancer, focusing on the lipid alterations co-occurring during tumorigenesis. The value of precision technologies and its application to target lipid metabolism in cancer will also be discussed. The degree to which lipid alterations, together with current therapies and intake of specific dietary components, affect risk of cancer is now under investigation, and innovative therapeutic or preventive applications must be explored.

Keywords: lipid metabolism, cancer prognosis, tumor microenviroment (TME), obesity, cancer risk, precision medicine, precision nutrition

INTRODUCTION

Cancer is a significant public health problem and is the second leading cause of death globally (1). The World Health Organization (WHO) has indicated that lung, prostate, colorectal (CRC), stomach, and liver cancers are among the most frequent types of cancer in men, whereas breast, CRC, lung, cervical, and thyroid cancers are the most frequent among women. Together with the genetic alterations, environmental factors orchestrate the multifactorial and multistage characteristics of cancer, modulating the expression of both tumor suppressor genes and oncogenes.

One of the hallmarks of cancer is the abnormal regulation of cellular metabolism (2). Tumor cells exhibit high rates of aerobic glycolysis and an increased anabolism to support growth, proliferation, and survival. Consequently, metabolism-related pathways have acquired enormous relevance in cancer research. Together with the Warburg effect and the increased glutaminolysis, lipid metabolism plays a key role in cancer metabolic reprogramming (3). Lipids, a highly diverse class of biological molecules, exert three main functions in the cells. First, they are employed for energy storage, principally as triacylglycerol esters and steryl esters, in lipid droplets (LDs). In addition, lipids are structural components of cellular membranes, and they also operate as metabolic signaling messengers (4). The sterol regulatory element-binding proteins (SREBPs) are transcription factors that coordinate and regulate the synthesis of lipids. They act in response to upstream signaling networks and to the intracellular nutrient status, to regulate the expression of enzymes involved in cholesterol and fatty acid (FA) synthesis and uptake (5).

Together with genetic alterations mediating the metabolic reprogramming in a cell autonomous manner, cancer progression and dissemination also depend on the availability of nutrients and oxygen at the tumor microenvironment. Tumors communicate with the surrounding microenvironment, which includes fibroblasts, adipocytes, immune cells, endothelial cells, and components of the extracellular matrix—to support cancer proliferation and dissemination (6).

Furthermore, key lipid metabolism genes have been proposed as prognostic biomarkers in several types of cancer associated with tumor recurrence and/or survival (7, 8). Indeed, the role of lipid metabolism alterations in tumor cell migration, invasion, and angiogenesis has been clearly demonstrated (9–11).

The technical improvement and development of "omics" approaches, together with the availability of large public accessible databases, have redefined current strategies of cancer research (12) allowing to reanalyze, recapitulate, and update our knowledge of the relevance of lipid metabolism–related genes in cancer. Genomics and transcriptomics are being applied for precision medicine purposes in cancer. The design, validation, and use of polygenetic scores open a window of new opportunities to integrate "omics" technologies into clinical advice. Moreover, proteomics, metabolomics, lipidomics, and metagenomics will complete the full scenario (13). Additionally, clinical trials combining current chemotherapies with natural bioactive compounds toward altered lipid metabolism represent a promising strategy to improve cancer treatment (14).

In this review, we will discuss about the role of lipid metabolism alterations in cancer. We will explore their mechanism of action and their oncologic implications. Moreover, we will analyze current reports and knowledge of lipid metabolism biomarkers in the most frequent types of cancer. Finally, we will investigate their emergent use in precision medicine and precision nutrition strategies.

IMPACT OF OBESITY IN CANCER

In recent years, it has demonstrated that cancer malignancy not only relays on the genetic factors—oncogenic and tumor suppressor alterations—from patients, but also on environmental factors associated with lifestyle (15). In this regard, it has been shown that up to one-third of cancer deaths could be prevented by modifying environmental factors related to lifestyle such as physical activity and diet, alcohol consumption, and smoking. Unhealthy diets—high consumption of saturated FAs or high-glucose-content beverages—are also associated with the development of systemic metabolic alterations including obesity, insulin resistance, and metabolic syndrome, among others. Obesity, which is defined as a high body weight with excessive adipose tissue accumulation, can be considered as a chronic, multifactorial, and proinflammatory disease (6, 16). Obesity is a risk factor for several chronic diseases including type 2 diabetes mellitus, cardiovascular diseases, hepatic steatosis, and cancer initiation and progression (17, 18). In fact, the overall risk of cancer death is around 1.5- to 1.6-fold in individuals with a body mass index higher than 40 kg/m^2 (19). The main types of cancer where obesity has been found associated with are prostate cancer (20), postmenstrual endometrial (21), breast cancer (22), ovary (23), bladder (24), liver (25), colon (26), and pancreas (22). During obesity, adipocytes accumulate in locations not classically associated with adipose tissue. Fat accumulation in ectopic sites is classified as central adipose tissue with systemic effects and locally accumulated adipose tissue supporting tumor microenvironment. The central adipose tissue leads to alterations in the levels of steroidal sex hormones, decreased insulin sensitivity, and low-grade inflammation (27), and it has been associated mainly with CRC (27) and breast cancer (6, 28). In addition, visceral depots of adipose tissue may provoke alterations in the cellular composition of cells surrounding the tumor microenvironment contributing to tumor cell proliferation and dissemination such as in the case of tumors located close to adipose tissues, such as breast, ovary, or colon tumors (6, 29).

The effects of tumor cells at the tumor microenvironment has been also found to associate with drug resistance (30). Cancer-associated adipocytes present metabolic features that sustain tumor progression and dissemination, because of the release of FAs and proinflammatory mediators, which contribute to support the surrounding tumor microenvironment (6). Thus, ovarian cancer partially relies on lipids provided by adipocytes at the tumor microenvironment (29, 31). Moreover, the hyperplasia and hypertrophy of adipose tissue diminish the levels of oxygen available, promoting angiogenesis, which may contribute to tumor dissemination (32). In this regard, breast, gastric, and colon cancers preferentially grow in adipocyte-enriched environments. In addition, excess of adipose tissue induces low chronic inflammation augmenting the circulating levels of proinflammatory interleukins (IL-6 and IL-8), tumor necrosis factor α, vascular endothelial growth factor (VEGF), and prostaglandins and leukotrienes, which have protumorigenic effects. Arachidonic acid (AA) is the main precursor of proinflammatory lipid mediators,

such as prostaglandins, thromboxanes, and leukotrienes, which promote proliferation, cell survival, and dissemination of cancer cells. Inflammatory prostaglandins, such as prostaglandin E_2 produced by COX2 (cyclooxygenase 2), activate epidermal growth factor receptor cell signaling to promote angiogenesis and the expression of matrix metalloproteases in colon cancer (33). Prostaglandins have been shown to inhibit the antitumor immune response by diminishing the activation of cytotoxic $CD8^+$ T lymphocytes and the infiltration of natural killer cells and dendritic cells to the tumor (34). In this regard, COX2 inhibitors have been demonstrated to augment the response to immune checkpoint inhibitors in melanomas (35, 36).

In addition, it has been described that obese individuals present an altered gut microbiota and disrupted intestinal epithelium barrier. Dysbiosis is associated with microbial diversity together with an increase in proinflammatory species. Intestinal dysbiosis has been associated with gastric, CRC, and esophageal cancers (37, 38). Thus, the design of microbiota-targeting therapies is now considered as a feasible strategy in the clinic.

Because of the important metabolic link between obesity and the tumorigenic process (**Figure 1**), effective control of the nutritional and metabolic status of individuals (control of glucose, lipid levels, blood pressure, and chronic inflammation) might represent a specific and mechanistic approach to prevent and/or ameliorate cancer progression. In this scenario, precision nutrition has emerged as a complementary therapeutic tool in the management of metabolic alterations associated with cancer prognosis. Personalized nutrition compiles nutrigenetics (genetic variants and epigenetic signatures), deep phenotyping, and a wide spectrum of data concerning metabolic personalization through omics technologies—transcriptomics, metabolomics, lipidomics, and metagenomics. Importantly, nutritional interventions based on the knowledge of how nutrients and bioactive dietary compounds interact with the genome, metabolism, microbiome, etc., at the molecular level, represent an effective tool to fight against metabolic alterations.

LIPID METABOLIC REPROGRAMMING OF ONCOGENIC PATHWAYS IN CANCER

Cancer cells present metabolic alterations to provide the additional requirements of energy and metabolites for cancer cell proliferation and dissemination (2). Enormous diversity exists between the different types of cancer, and even within the same tumor. Moreover, cancer cells are characterized by the continuous capacity to adapt to changes in the levels of nutrients and oxygen at the tumor microenvironment (6). The altered tumor metabolism depends not only on the cell autonomous genetic alterations, but also on additional factors including diet, food behavior, exercise, and microbiome. All these factors together will determine the biology of the developing tumor (39) (**Figure 1**).

One of the most frequent metabolic alterations observed in cancer is the increased of the glycolytic pathway, independently of the oxygen levels (Warburg effect) (40). Aerobic glycolysis

in cancer is coupled to increase glutamine metabolism for the anaplerosis of intermediated of the tricarboxylic acid (TCA) cycle (41). In addition, different studies including *in vitro*, preclinical, and clinical trials have demonstrated the relevance of lipid metabolism to sustain cancer initiation and progression (6). The inhibition of lipid metabolic enzymes has been shown to induce tumor regression, to inhibit the metastatic spread, and/or to avoid drug resistance. Lipids not only are structural components of biological membranes, but also provide energy by means of β-FA oxidation (β-FAO), control the redox homeostasis, and act as signaling molecules affecting a plethora of crucial processes in cancer including proliferation, migration, invasion, transformation, tumor microenvironment reshaping, and/or modulation of inflammation (42). Cholesterol is a key component of the cell membranes affecting its fluidity, stabilizing specific areas (lipid rafts) to transduce intracellular cell signaling pathways (43), and being precursor of steroidal hormones (44). In addition, lipids are also signaling molecules such as proinflammatory prostaglandins or tromboxanes—synthesized from omega-6 AA (45), or anti-inflammatory omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid, which availability depends on lipids provided from diet.
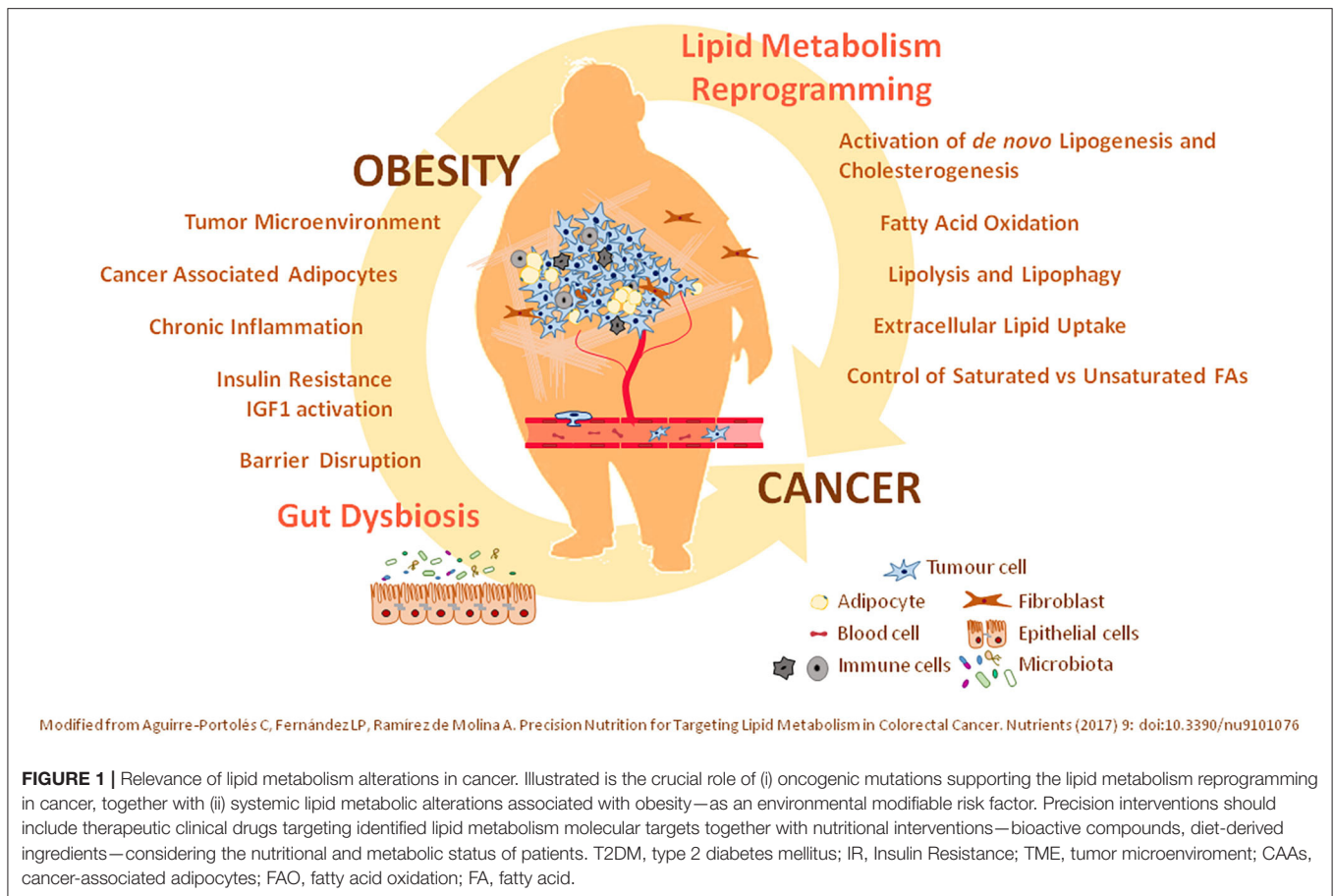
Herein, we describe potential strategies to target the altered lipid metabolism in cancer. In addition, as the uptake of high levels of saturated FAs from diet is a risk factor in several types of cancers, strategies to diminish lipolysis and promotion of healthy diets should also be considered.

Activation of *de novo* Lipogenesis and Cholesterogenesis

Lipid metabolism alterations affect not only tumor cell proliferation, but also dissemination and resistance to chemotherapeutic drugs (46). Most of adult tissues obtain FAs, cholesterol, and lipids from diet; meanwhile, *de novo* synthesis of FAs and cholesterol is restricted to the liver and adipocytes. Tumors frequently present the capability to activate the *de novo* synthesis of cholesterol and FAs (47) making them more independent from externally provided lipids (48, 49). Importantly, targeting enzymes associated with *de novo* lipogenesis and/or the mevalonate pathway has been shown to inhibit tumor growth (6, 50).

FAs are synthesized from cytoplasmic acetyl-CoA (AcCoA), generated from citrate produced from glucose, glutamine, or acetate (48). ATP-citrate lyase (ACLY) generates AcCoA and oxaloacetate (OAA) from citrate (48, 51). AcCoA carboxylases (ACC1/2) carboxylase AcCoA to form malonyl-CoA. Subsequent condensation steps, catalyzed by FA synthase (FASN), forms the 16-carbon saturated FA palmitate. Palmitate is then elongated by FA elongases (ELOVL) and desaturated by stearoyl-CoA desaturase (*SCD1*) or FA desaturases (FADS) to form other nonessential FAs, such as the 18-carbon monounsaturated FA (MUFA) oleate (C18:1) (**Figure 2**).

Many enzymes implicated in *de novo* synthesis of FAs and cholesterol have been proposed as biomarkers for prognosis in specific types of cancer. FASN is found upregulated in prostate and breast cancer (47, 52), and ACLY has been shown to support

FIGURE 1 | Relevance of lipid metabolism alterations in cancer. Illustrated is the crucial role of (i) oncogenic mutations supporting the lipid metabolism reprogramming in cancer, together with (ii) systemic lipid metabolic alterations associated with obesity—as an environmental modifiable risk factor. Precision interventions should include therapeutic clinical drugs targeting identified lipid metabolism molecular targets together with nutritional interventions—bioactive compounds, diet-derived ingredients—considering the nutritional and metabolic status of patients. T2DM, type 2 diabetes mellitus; IR, Insulin Resistance; TME, tumor microenviroment; CAAs, cancer-associated adipocytes; FAO, fatty acid oxidation; FA, fatty acid.

tumor formation and transformation (51). Inhibition of several enzymes of *de novo* lipogenesis, such as FASN, and ACC1 and ACC2, has been tested in different cancer models showing their relevance on tumor growth inhibition (53).

Similarly, inhibition of hydroxymethylglutaryl-CoA (HMGCoA) reductase (HMGCR), by statins, leads to inhibition of cell proliferation of breast cancer cells (54) and tumor regression in several preclinical mouse models, and it is being tested in clinical trials (43). The overexpression of enzymes of the mevalonate pathway has been proposed as biomarkers of poor prognosis in breast cancer (55). Cholesterol is generated by the mevalonate pathway, by condensation of two AcCoA molecules to form 3-HMGCoA, which is then reduced to form mevalonate, and then isoprenoid farnesyl-pyrophosphate. Several studies have shown that targeting the synthesis of cholesterol inhibits cancer cell proliferation and transformation (56).

De novo synthesis of FAs and cholesterogenesis are transcriptionally regulated by SREBPs, which are downstream oncogenic pathways including PI3K/Akt (57) and c-Myc (47) (**Figure 2**).

The SREBP family includes three transcription factors: SREBP1a and SREBP1c, which are derived from *SREBF1* gene by alternative splicing (58), and SREBP2, which is encoded by *SREBF2* gene. SREBPs are bound to the endoplasmic reticulum (ER) as inactive precursors (59). When the intracellular levels of cholesterol are high, insulin-induced genes interact with

SREBP-cleavage–activating proteins (SCAPs) to retain SREBP inactive precursors attached to the ER. When cholesterol levels are low, SCAPs facilitate the translocation SREBPs to the Golgi apparatus to be further processed releasing the active forms (56). SREBP1 promotes the expression of lipogenic genes; meanwhile, SREBP2 regulates the expression of genes involved in the synthesis, uptake, and efflux of cholesterol. Nevertheless, SREBP1 and SREBP2 have overlapping activities. Both SREBP1 and SREBP2 are found overexpressed in several cancers. Regulation of the intracellular content of cholesterol has also been shown crucial for cancer cell survival. The ATP-binding cassette transporter (ABCA1) controls the efflux of cholesterol to ApoA-coated lipoproteins (57). Recently, it has been demonstrated that activation of p53 increases the retrograde transport of cholesterol from the plasma membrane to the ER, to prevent SREBP2 maturation (60). In addition, cholesterol levels are fine tune regulated by microRNA33—encoded by an intron within the *SREBF2* gene (51)—which targets ABCA1. In addition, the esterification of cholesterol for storage in LDs, by sterol *O*-acyltransferase 1 (ACAT1), has been shown to augment the survival in prostate cancer (61).

Fatty Acid Oxidation in Cancer

In addition to *de novo* synthesis of FAs and cholesterol, the mobilization of intracellular FAs for FAO at mitochondria is crucial for cancer survival and dissemination. It is well-known
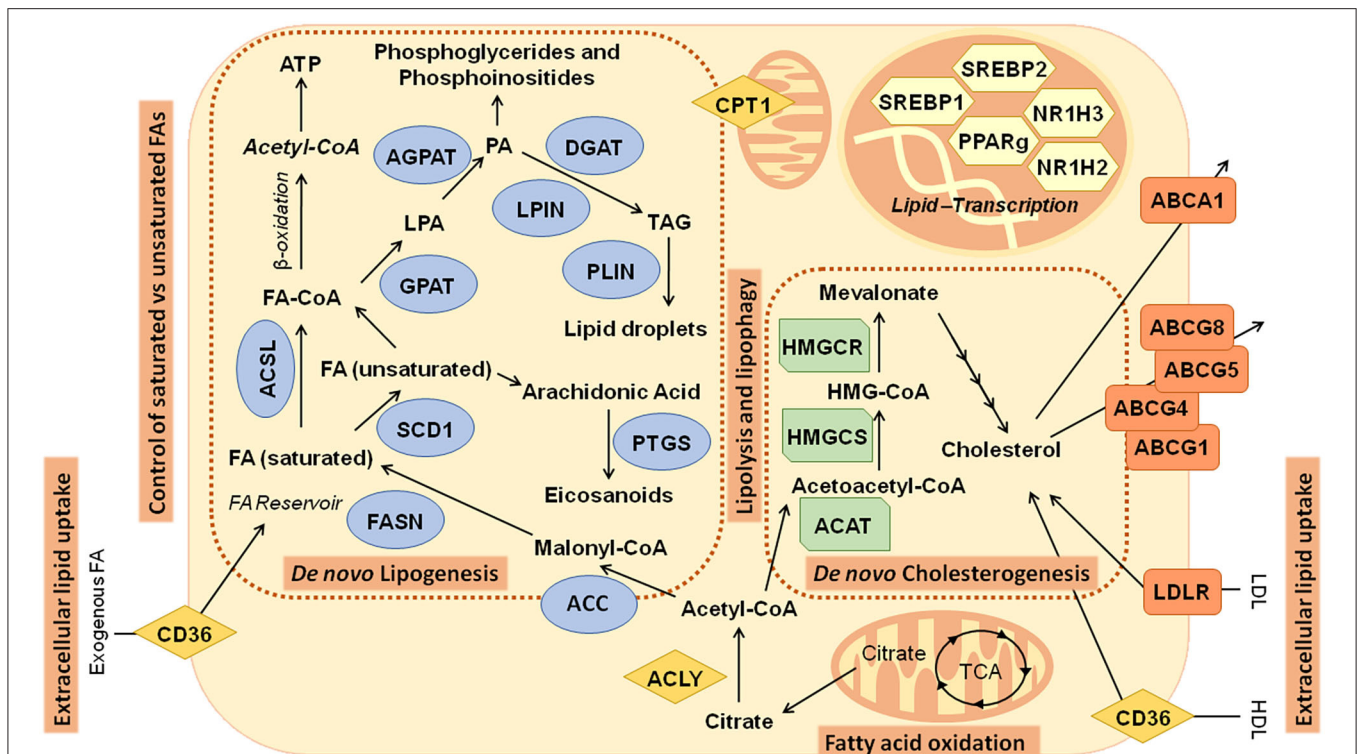
FIGURE 2 | Main metabolic pathways related to lipid metabolism in cancer: Illustration of pathways and genes implicated in *de novo* lipogenesis—fatty acids and cholesterol biosynthesis. ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; ABCG4, ATP-binding cassette subfamily G member 4; ABCG5, ATP-binding cassette subfamily G member 5; ABCG8, ATP-binding cassette subfamily G member 8; ACAT, acetyl-CoA acetyltransferase; ACC, acetyl- CoA carboxylase; ACLY, ATP citrate lyase; ACSL, acyl-CoA synthetase long chain; AGPAT, 1-acylglycerol-3-phosphate *O*-acyltransferase; CD36, CD36 molecule; CPT1, carnitine palmitoyltransferase; DGAT, diacylglycerol *O*-acyltransferase; FA, Fatty acids; FASN, fatty acid synthase; GPAT, glycerol-3-phosphate acyltransferase; HDL, high-density lipoprotein; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HMGCS, 3-hydroxy-3-methylglutaryl-CoA synthase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPIN, Lipin; NR1H2, nuclear receptor subfamily 1 group H member 2; NR1H3, nuclear receptor subfamily 1 group H member 3; PLIN, perilipin; PPARγ, peroxisome proliferator-activated receptor γ; PTGS, prostaglandin-endoperoxide synthase; SCD1, stearoyl-CoA desaturase; SREBP1, Sterol regulatory element binding transcription factor 1; SREBP2, sterol regulatory element binding transcription factor 2; TCA, tricarboxylic acid cycle.

that tumor cells present higher levels of reactive oxygen species (ROS) than not tumor cells, which allow them to activate prosurvival and epithelial-to-mesenchymal transition programs to support cancer progression and dissemination. Nevertheless, excessive ROS may promote apoptotic cell death. It has been demonstrated that enzymes implicated in the mobilization of intracellular neutral lipids provide metabolic flexibility to increase the levels of FAs for oxidation at mitochondria. In the FAO pathway, acyl-CoAs are cyclically dehydrogenated, hydrated, and decarboxylated, resulting in the progressive shortening of the FA, together with the production of NADH and FADH$_2$ and AcCoA. NADH and FADH$_2$ will be used for ATP production in the electron transport chain, and AcCoA can enter the Krebs cycle. AcCoA together with OAA gives rise to citrate, which after being exported to cytoplasm, can enter two metabolic pathways to produce cytosolic NADPH (62).

Enhanced mitochondrial β-oxidation of FAs has been described in pancreatic cancer (63, 64) and in metastatic breast cancer (65). FAO not only provides energy when glucose becomes limiting, but it also contributes to a better control of the oxidative

stress, by augmenting the intracellular levels of NADPH (66). Increased FAO augments survival in leukemia and gliomas by counteracting the metabolic oxidative stress. Moreover, FAO has been shown crucial for the survival of cells from solid tumors when undergoing loss of attachment, which triggers *anoikis* or cell death due to oxidative stress (67, 68).

In addition, FAO is also influenced by the tumor microenvironment such as in the case of ovarian cancers, which preferentially metastasizes to the omentum enriched in adipocytes, which provides lipids for ATP and NADPH production to control metabolic stress during metastasis.

Regulation of FA Storage and Intracellular FA Mobilization (Lipolysis and Lipophagy)

De novo synthesis of FAs in cancer cells is coupled to additional processes to accommodate the increase in the intracellular lipid content, to preserve the homeostasis between lipid storage and lipid mobilization (69). FAs from *de novo* lipogenesis are accumulated into neutral lipids (stored in LDs) and phospholipids (in membranes). LDs are complex and dynamic

organelles consisting of a neutral lipid core surrounded by a phospholipid monolayer and a complex proteome associated. LDs itself have been proposed as novel diagnostic biomarkers for glioblastoma. It has been demonstrated that while they are not detectable in low-grade gliomas or normal brain tissues, they are common in glioblastoma, the most lethal brain tumor (70). Among the LD-associated proteins, there are enzymes of the sterol biosynthetic pathway, the acyl-CoA metabolism (ACSLs), and triacylglycerol (TAG) biosynthesis. Structural proteins, such as perilipins (PLINs) or caveolins, are critical for the integrity of LDs to avoid collapse and to protect them from lipolysis (**Figure 2**). Cancer cells present higher amounts of LDs than normal cells (71). Increased expression of PLIN2 has been shown to favor the accumulation of LDs (72), contributing to a better control of the ER stress, to increase the protection against ROS, and to augment the resistance to therapeutic drugs in cancer cells. On the contrary, PLIN2 depletion significantly attenuated the proliferation of colon cancer cells (73), supporting the LD-associated proteins as potential druggable targets for cancer treatment (11).

The increase in *de novo* synthesis of FAs in cancer cells requires efficient and complementary lipolytic mechanisms to accommodate the intracellular lipid content. Thus, lipolysis allows the stored lipids to be available for the synthesis of phospholipids and lipid signaling mediators and/or to increase the levels of ATP or NADPH when required. Several enzymes involved in lipolysis—adipose TAG lipase (ATGL), hormone-sensitive lipase (HSL), monoacylglycerol lipase (MAGL)—have been described to promote tumorigenesis (74). In this sense, ATGL knockdown in HCT116 CRC cells reduced cell proliferation (75). Increased levels of MAGL are associated with aggressive cancer types such as melanoma and ovarian and breast cancer (74), and inhibition of MAGL suppresses cancer cell migration, invasion, and survival (76). Recently, it has been demonstrated that glioblastomas, which acquire large amounts of free FAs, upregulate diacylglycerol-acyltransferase 1 (DGAT1) to store the excess FAs into triglycerides and LDs (77). Inhibition of DGAT1 disrupted lipid homeostasis, resulting in increased levels of ROS leading to apoptotic cell death.

In addition, a specific function of autophagy associated with the regulation of the intracellular lipid content—lipophagy—has been described to augment resistance to cell death in cancer (78).

Extracellular Lipid Uptake

In addition, similar to normal cells, cancer cells can uptake exogenous lipids when *de novo* lipogenesis is inhibited. Upregulation of cell surface receptors, such as cluster of differentiation 36 (CD36) (**Figure 2**), has been found to augment metastasis (79, 80). CD36 inhibition diminished tumor growth and metastasis in preclinical models of prostate cancer (80). Moreover, the expression of low-density lipoprotein receptor (LDLR) for the internalization of low-density lipoproteins (LDLs) has been found upregulated in renal cell carcinoma (RCC) cells (81). FA-binding proteins (FABPs) contribute to augment the lipid uptake, as well as the intracellular lipid trafficking in cancer cells (82). In breast cancer and glioblastoma cell lines, it has been shown that the uptake of extracellular

FAs during hypoxia is sustained by the upregulation of FABP3 and FABP7; meanwhile, FABP5 increases cell proliferation and growth in prostate cancer (83).

Control of Saturated vs. Unsaturated FAs

Depending on the source of FAs, *de novo* lipogenesis or extracellular lipid uptake, the levels of saturated FAs incorporated in the phospholipids of cell membranes are different. The lipogenic pathway increases the saturation level of cell membranes with saturated and MUFAs (84), which are less sensitive to suffer lipid peroxidation compared to polyunsaturated acyl chains (PUFAs) mainly obtained from diet. This way, *de novo* lipogenesis contributes to augment the resistance to oxidative stress and chemotherapy in cancer cells (85).

Nevertheless, excessive accumulation of saturated FAs in the cell membranes can lead to lipotoxicity. In this regard, SCD1 inhibition induces ER stress and apoptosis in cancer cells and diminishes the tumor growth in xenografts models of colon and lung cancers (86). During tumor growth, inner parts of the tumors are faced to hypoxia and reduced nutrient availability. Tumors have developed different strategies to balance the levels of saturated vs. unsaturated FAs. Thus, tumors anticipate lipotoxicity by augmenting the uptake of MUFAs/PUFAs from plasma, which are further stored into LDs or incorporated into phospholipids at the cell membranes. As SCD1 activity requires oxygen, during hypoxia some tumors rely on the activity of DGATs to incorporate MUFAs into TG, which are further accumulated into LDs (**Figure 2**). In addition, tumors balance, via the Lands cycle, the levels of saturated vs. unsaturated FAs in the phospholipids at the cell membranes. Recently, a process known as ferroptosis has been described associated with high levels of MUFA/PUFAs in the phospholipids of cell membranes, which induce cell death by means of their oxidation through the Fenton pathway. Long-chain FA acyl CoA synthetases (ACSLs)—implicated in the long chain FA activation—may control ferroptosis, as distinct isoforms use distinct substrates. Meanwhile, ACSL4 has PUFAS as main substrates such as AA, ACSL3 can activate both MUFAs and PUFAs, allowing a better control of the excessive accumulation of PUFAs in phospholipids (87). In addition, ACSL3 allows a better control of FA distribution between LD storage or β-FAO, providing a better control of the oxidative stress (42).

LIPID METABOLISM ALTERATIONS AND CANCER PROGNOSIS

Alterations of lipid metabolism genes are found in many tumor types, predominantly, but not exclusively, because lipid metabolism can modulate different cellular processes that go from plasmatic and organelle membrane organization and plasticity (88, 89), substrate supply for ATP synthesis, (62) and intracellular cell signaling activation (90). Cancer tissues display abnormal activation of *de novo* lipogenesis and cholesterogenesis (91). Extremely proliferative cancer cells exhibit an intense lipid and cholesterol avidity, which they satisfy by increasing

TABLE 1 | Prognostic value of lipid metabolism–related genes.

Prognostic value	Literature								The Cancer Genome Atlas (TCGA)-The Protein Atlas																
	LC		CRC		BC		PC		LC	CRC	BC	PC	CC	EC	G	HNC	LC	M	OC	PC	RC	SC	TC	ThC	UC
Fatty acid–related pathways																									
Fatty acid synthesis																									
ACLY	red	(61, 102, 103)	red	(104)									red				red								
pACC	green	(105)	green	(39)																					
ACACA																	red								
ACACB			green	(106)																green	green				
FASN	red	(107)	red	(36, 108–112)	red	(113–115)	red	(116–119)					red								red				
ACSL1			red	(7–9, 120, 121)																	green				
ACSL3	red	(+)							red								red								
ACSL4			red	(7–9, 120, 121)	red	(122)																			green
ACSL5					green	(121, 123)									green										
ACSL6																									
SCD1	red	(124)	red	(7, 125)	red	(126)															red				red
FADS1	red	(127)																			red			red	red
FADS2																					red				red
FADS3																red					red				
FADS4																					green				
FADS6																									
FADS7														red			red				red				red
FADS8																					green				green
PTGS1																					red				red
PTGS2	red	(128–130)	red	(131)	red	(132)	red	(133)													red				
GPAT1																					green				
GPAT2																									
GPAT3																					green				red
GPAT4													red	green					red		red				green
AGPAT1	red	(7, 8)										red	red												
AGPAT2																									
AGPAT3														red							green				
AGPAT4													red								red				
AGPAT5															green			red							
LPIN1	red	(134)			green	(135)	red	(136)																	
LPIN2																green									
LPIN3													red						red		red				

(Continued)

TABLE 1 | Continued

Prognostic value	Literature								The Cancer Genome Atlas (TCGA)-The Protein Atlas																
	LC		CRC		BC		PC		LC	CRC	BC	PC	CC	EC	G	HNC	LC	M	OC	PC	RC	SC	TC	ThC	UC
PLIN1	red	(137)			green	(138)																		green	
PLIN2					green	(139)															red			green	
PLIN3										red					green		red				red				
PLIN4										red				red							red				
PLIN5											green			red			green				green				green
DGAT1																									
DGAT2					green	(140)											red								
Fatty acids–related transportation																									
CD36			red	(141)	red	(141)	red	(141)														red			
CPT1A					red	(142, 143)							red								green				
CPT1B																									
CPT1C																				green					
Cholesterol-related pathways																									
Cholesterol synthesis																									
ACAT1							red	(144, 145)									green				green				
ACAT2										green				red							red				
HMGCS1																									
HMGCS2			red	(146)			red	(147)									green	green			green				
HMGCR			green	(148)	green	(149, 150)															green				
Cholesterol-related transportation																									
ABCA1			red	(7, 8, 151)																					
ABCG1																					green				
ABCG4	red	(152)																							
ABCG5			red	(153)														green							
ABCG8																									
LDLR			green	(154)																red	red				red
Lipid transcription																									
Transcription factors																									
SREBP1					red	(155)								green						green					
SREBP2			red	(156)			red	(157)													green				
PPARγ	green	(158, 159)	green	(160)	green	(161, 162)	green	(163)												red	green				green

(Continued)

TABLE 1 | Continued

Prognostic value	Literature				The Cancer Genome Atlas (TCGA)–The Protein Atlas																
	LC	CRC	PC	BC	LC	CRC	PC	BC	CC	EC	G	HNC	LC	M	OC	PC	RC	SC	TC	ThC	UC
NR1H2		(156)																			
NR1H3	(164)	(156)								EC			LC				RC				UC

Favorable
Unfavorable

Gene prognostic value reported in the literature in most frequent types of cancer according to the World Health Organization (WHO) together with gene prognostic value using data from The Cancer Genome Atlas (TCGA) and visualized using The Pathology Atlas online tool. Abbreviations: LC, lung cancer; CRC, colorectal cancer; BC, breast cancer; PC, prostate cancer; CC, cervical cancer; EC, endometrial cancer; G, glioma; HNC, head and neck cancer; LC, liver cancer; M, melanoma; OC, ovarian cancer; PC, pancreatic cancer; RN, renal cancer; SC, stomach cancer; TC, testis cancer; ThC, thyroid cancer; UC, urothelial cancer; ACLY, ATP citrate lyase; pACC, phospo acetyl-CoA carboxylase; ACACA, acetyl-CoA carboxylase A; ACACB, acetyl-CoA carboxylase B; FASN, fatty acid synthase; ACSL1, acyl-CoA synthetase long chain family member 1; ACSL3, acyl-CoA synthetase long chain family member 3; ACSL4, acyl-CoA synthetase long chain family member 4; ACSL5, acyl-CoA synthetase long chain family member 5; ACSL6, acyl-CoA synthetase long chain family member 6; SCD1, stearoyl-CoA desaturase1; FADS1, fatty acid desaturase 1; FADS2, fatty acid desaturase 2; FADS3, fatty acid desaturase 3; FADS4, fatty acid desaturase 4; FADS6, fatty acid desaturase 6; FADS7, fatty acid desaturase 7; FADS8, fatty acid desaturase 8; PTGS1, prostaglandin-endoperoxide synthase 1; PTGS2, prostaglandin-endoperoxide synthase 2; GPAT1, glycerol-3-phosphate acyltransferase 1; GPAT2, glycerol-3-phosphate acyltransferase 2; GPAT3, glycerol-3-phosphate acyltransferase 3; GPAT4, glycerol-3-phosphate acyltransferase 4; AGPAT1, 1-acylglycerol-3-phosphate O-acyltransferase 1; AGPAT2, 1-acylglycerol-3-phosphate O-acyltransferase 2; AGPAT3, 1-acylglycerol-3-phosphate O-acyltransferase 3; AGPAT4, 1-acylglycerol-3-phosphate O-acyltransferase 4; AGPAT5, 1-acylglycerol-3-phosphate O-acyltransferase 5; LPIN1, lipin 1; LPIN2, lipin 2; LPIN3, lipin 3; PLIN1, perilipin 1; PLIN2, perilipin 2; PLIN3, perilipin 3; PLIN4, perilipin 4; PLIN5, perilipin 5; DGAT1, diacylglycerol O-acyltransferase 1; DGAT2, diacylglycerol O-acyltransferase 2; CD36, CD36 molecule; CPT1A, carnitine palmitoyltransferase 1A; CPT1B, carnitine palmitoyltransferase 1B; CPT1C, carnitine palmitoyltransferase 1C; ACAT1, acetyl-CoA acetyltransferase 1; ACAT2, acetyl-CoA acetyltransferase 2; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; ABCG4, ATP-binding cassette subfamily G member 4; ABCG5, ATP-binding cassette subfamily G member 5; ABCG8, ATP-binding cassette subfamily G member 8; LDLR, low-density lipoprotein receptor; SREBP1, Sterol regulatory element binding transcription factor 1; SREBP2, Sterol regulatory element binding transcription factor 2; PPARγ, peroxisome proliferator-activated receptor γ; NR1H2, nuclear receptor subfamily 1 group H member 2; NR1H3, nuclear receptor subfamily 1 group H member 3. (+) Unpublished results.

the uptake of dietary or exogenous lipids and lipoproteins or activating lipogenesis or cholesterol synthesis (3). Importantly, this aberrant lipid metabolism does not only influence the primary tumor, but the exogenous lipids produced by tumor microenvironment can also influence malignancy (14, 92–95). Besides, three basic steps during metastasis: migration (96), invasion (9, 10) and angiogenesis (97, 98), are affected by lipid metabolism regulation (11).

Nowadays, there are increasing evidences of the role of lipid metabolism alterations as biomarkers of cancer prognosis and survival. Here, we are going to review previous knowledge on the prognostic value of lipid-related genes that belong to FAs and cholesterol pathways (**Figure 2**) in the most frequent types of cancer according to the WHO: lung, CRC, breast, and prostate.

Furthermore, "omics" data publicly available in huge searchable databases facilitate addressing specific medical issues in thousands of patients. Remarkably, The Cancer Genome Atlas (TCGA) gene expression dataset (https://www.cancer.gov/tcga) and The Human Protein Atlas website together with The Pathology Atlas online tool (https://www.proteinatlas.org/humanproteome/pathology), which contains mRNA data from TCGA study and protein expression data from different forms of human cancer (99–101), allowing us to obtain a global view of the putative implications of lipid metabolism–related genes in cancer prognosis. Data from TCGA visualized using The Pathology Atlas online tool, are summarized in **Table 1**.

Fatty Acid–Related Alterations as Biomarkers of Cancer Prognosis and Survival

De novo FA biosynthesis occurs in the cellular cytoplasm. FAs originate from acetyl-coenzyme A, which is mostly provided by citrate produced by the TCA cycle. Switch of citrate into AcCoA is catalyzed by ATP citrate lyase (ACLY) (**Figure 2**). Consequently, ACLY is a key enzyme connecting carbohydrate to lipid metabolism by producing AcCoA from citrate for both FA and cholesterol synthesis (61). Several studies have associated ACLY expression in tumor tissues with worse prognosis. ACLY overexpression correlated with stage, differentiation grade, and a poorer prognosis in non–small cell lung cancer (NSCLC) (61). Besides, in combination with the glucose transporter *GLUT1, ACLY* was also an independent prognostic factor for overall survival (OS) in node-negative patients with NSCLC (102). However, one study reports that young NSCLC patients overexpressing *ACLY* had longer OS, in contrast to older patients where overexpression of ACLY appears to predict the opposite prognosis (103). *ACLY* also facilitates colon cancer cell metastasis, and high expression levels of *ACLY* and Catenin β1 (*CTNNB1*) protein were positively correlated with metastasis of colon cancer (104). Data from TCGA showed *ACLY* as a putative unfavorable marker of cervical and liver cancer (**Table 1**).

At the genomic level, single nucleotide polymorphisms (SNPs) in *ACLY* gene have been described as independent cancer prognostic markers in Asiatic populations. SNP rs9912300 in *ACLY* gene was significantly associated with OS in lung cancer patients (165). rs9912300 and rs2304497, both functional *ACLY*

SNPs, exhibited a significant association with risks of death and recurrence in patients with advanced stages of colon cancer (166).

The following step of FA biosynthesis involves the activation of AcCoA to malonyl-CoA, which is catalyzed by AcCoA carboxylase (ACC) (**Figure 2**). ACC is a complex multifunctional enzyme system. There are two ACC forms, α (ACACA) and β (ACACB), encoded by two different genes. High phospho-acetylCoA carboxylase (pACC) was an independent marker for prediction of better survival in lung adenocarcinoma patients (105), and low pACC levels detected by immunohistochemistry were associated both with worse OS and progression-free survival in advanced stage CRC (167). In the same line, gene expression analysis reported that patients with upregulation of six of these hub genes (genes with high correlation in candidate modules) (*ACACB*, acyl-CoA dehydrogenase medium chain, adiponectin, *C1Q* and collagen domain containing, acyl-CoA synthetase short-chain family member 2, phosphoenolpyruvate carboxykinase 1 and PLIN1) displayed improved breast cancer prognosis (106). In TCGA dataset, *ACACA* gene expression is an unfavorable risk factor for liver cancer, whereas *ACACB* is a favorable prognostic factor for both renal and pancreas tumors (**Table 1**). Finally, it has been described in prostate cancer that genetic alterations of *ACACA*, *FASN*, and *SREBF1* predicted worse overall patient survival (168).

Malonyl-CoA is coupled to the multifunctional enzyme FASN. Repeated cycles of acetyl group's condensation produce the primary FA palmitate that can suffer separate elongation and/or unsaturation cycles to yield other FA molecules (169) (**Figure 2**). FASN is the key enzyme necessary for the *de novo* synthesis of long-chain FAs. FASN has been found overexpressed in nearly all of cancer tissues, and its expression is associated with a poorer prognosis.

One study reported that *FASN* gene expression was higher in the adjacent non-cancer tissue than in the NSCLC tissue, but authors concluded that it was a weaker predictor of shorter patient survival (170). However, a correlation analysis between expression levels of CD276 (B7-H3) and FASN exhibited a positive correlation with poor prognosis in clinical lung cancer tissues (107).

FASN levels were clearly upregulated in CRC tissues with high expression of FASN significantly associated with lymph node metastasis (108), liver metastasis (109), TNM (tumor, node, metastasis) stage, and poor prognosis (36). Moreover, a significant association was shown between FASN and VEGF expression, suggesting the involvement of FAS in tumor angiogenesis (110). Interestingly, one study reported that, among non-obese patients with colon cancer, tumoral FASN overexpression is associated with better survival, while among moderately overweight or obese patients, FASN overexpression may predict a poorer outcome (111). Furthermore, a panel of five genes including *FASN* (*ACOT8/ACSL5/FASN/HMGBCS2/SCD1*) has been reported to display a improved prognostic performance than validated clinical risk scales, and it is applicable for early discovery of CRC and tumor recurrence (112). Finally, FASN levels in serum were also examined in CRC patients, where it was associated with tumor stage (171), and high FASN levels are considered as a promising independent predictor of

CRC with advanced phases, late clinical stages, and shorter survival (172).

FASN is associated with poor prognosis in breast and prostate cancer, and its inhibition is selectively cytotoxic to human cancer cells (113). FASN was found overexpressed in most of the triple-negative breast cancer (TNBC) patients but not always correlated with OS or disease-free survival. High FASN was significantly associated with positive node status (114). A greater part of clinically HER2-positive tumors was achieved as FASN overexpressors. Reclassification of HER2-positive breast tumors based on FASN gene expression predicted a significantly inferior relapse-free and distant metastasis-free survival in HER2$^+$/FASN$^+$ patients (115).

A substantial subset of prostatic cancers displays clearly elevated expression of immunohistochemically detectable FASN, a feature that has been associated with poorer prognosis (116–119). Furthermore, high expression level of FASN resulted in a significantly poor prognosis of pancreatic cancer (173), and data from TCGA study suggest that *FASN* expression could be a marker of bad outcome in cervical and renal cancer (**Table 1**).

In addition, several genetic changes in *FASN* gene have been associated with cancer prognosis. Two SNPs rs4246444 and rs4485435 were significantly associated with the recurrence of NSCLC (165). Finally, as it has been previously mentioned in prostate cancer that genetic alterations of *FASN* together with *ACACA* and *SREBF1* predicted worse prognosis (168).

Then, FAs are activated with CoA by fatty acyl-CoA synthetases (ACSLs) (**Figure 2**), which is essential for phospholipid and triglyceride synthesis and lipid modification of proteins in addition to for FA β-oxidation (169).

Family of long-chain acyl-CoA synthetases has been extensively proposed as putative prognostic biomarkers of cancer. *ACSL3* is up-regulated in lung cancer compared to the healthy lung tissue (174), and recently, an association with *ACSL3* expression, NSCLC prognosis, and the efficacy of statins treatment has been discovered (L. P. Fernandez et al., unpublished results). *ACSL3* was also found to be overexpressed in estrogen receptor–negative breast cancer (175) and prostate cancer (176). *ACSL1* and *ACSL4* overexpression was associated with a poor clinical outcome in stage II CRC patients (7–9, 120, 121). In addition, *ACSL4* is considered a biomarker for liver and breast cancers (122, 177). By contrast, downregulation of *ACSL5* in breast cancer was associated with a poorer prognosis (121, 123). There have not been reported associations between *ACSL6* and cancer survival (178).

An *in silico* study (121) also suggested that high *ACSL1* expression was associated with worse outcome in lung cancer patients, and *ACSL3* overexpression was associated with worse survival in patients with melanoma. In contrast, high *ACSL3* expression predicted a better prognosis in ovarian cancer. In the same study, *ACSL4* overexpression predicted bad prognosis in CRC, but good prognosis in breast, brain, and lung cancers. High expression of *ACSL5* predicted good prognosis in breast, ovarian, and lung cancers. Finally, low *ACSL6* predicted a worse prognosis in acute myeloid leukemia. *In silico* analysis of TCGA data (**Table 1**) suggested that *ACSL1*, *ACSL4*, and *ACSL5* are associated with favorable outcome in renal, urothelial, and

endometrial cancers, respectively, whereas *ACSL3* expression predicts poor survival in lung and liver tumors.

Genetically, a 3′-UTR polymorphism in *ACSL1* is associated with *ACSL1* expression levels and poor clinical outcome in CRC patients (14, 120). Patients carrying the *ACSL1* T/T genotype had significantly reduced disease-free survival compared with patients carrying the C/T or C/C genotype, with 3-fold higher risk of recurrences. T/T genotype for rs8086 is correlated with worse clinical outcome and simultaneously associates with high *ACSL1* mRNA levels (14, 120).

Stearoyl CoA desaturase 1 (*SCD1*) catalyzes the rate-limiting step in the synthesis of MUFAs that are the main components of tissue lipids. *SCD1* has been associated with tumor development, late stage, and reduced survival in lung adenocarcinoma (124). Together with other three lipid metabolism–related genes (*ABCA1*, *ACSL1*, and *AGPAT1*), *SCD1* expression separated stage II colon cancer patients with a 5-fold higher risk of relapse (7). Moreover, positive associations between *SCD1* expression and CRC patient clinical status and the expression of cancer stem cell–related genes (*WNT* and *NOTCH* signaling) were found based on TCGA data analysis (125). In the same line, high *SCD1* expression is associated with shorter survival in breast cancer patients (126). **Table 1** shows that *SCD1* is an unfavorable marker of survival in renal and urothelial cancer in TCGA tumors. Other desaturases have also been analyzed as prognostic markers, and, for example, reduced expression of *FADS1* suggests pessimistic prognosis for NSCLC patients (127).

Glycerol-3-phosphate acyltransferase (GPAT) catalyzes the first step in the production of almost all membrane phospholipids. GPAT transfers an acyl group from acyl-CoA or acyl-ACP at the sn-1 or-2 position of glycerol 3-phosphate originating lysophosphatidic acids (LPAs) (179). LPA is a substrate for synthesis of numerous important glycerolipid intermediates, such as storage lipids, extracellular lipid polyesters, and membrane lipids (**Figure 2**). Four GPATs have been discovered; nevertheless, only GPAT1 (GPAM) has been related to cancer outcome. High GPAT1 expression has been associated with reduced OS in ovarian cancer (180). Data from TCGA suggested that *GPAT1* could be a favorable prognostic marker in renal cancer, while *GPAT3* is a putative biomarker of good prognosis in renal cancer in contrast to urothelial cancer. Finally, *GPAT4* expression could have a risk effect in ovarian and endometrial cancers, and a protective one in prostate and urothelial cancer (**Table 1**).

LPA is further metabolized to phosphatidic acid (PA) by AGPATs (1-acylglycerol-3-phosphate *O*-acyltransferases) (**Figure 2**). AGPAT1 belongs to previously mentioned transcriptional signature where combined analysis of four genes, *ABCA1*, *ACSL1*, *AGPAT1*, and *SCD1*, is associated with higher risk of relapse in stage II CRC patients (7). Furthermore, individuals with upregulation of *AGPAT1* expression have an increased risk of CRC recurrence, independently of tumor stage (8). Expression of *AGPAT2* was significantly related to decreased OS as well as to shorter progression-free survival in ovarian cancer patients younger than 60 years (181). When we consider tumors from TCGA study, several associations were found (**Table 1**). *AGPAT3* is a marker of good prognosis in renal cancer

and predicts bad outcome in cervical cancer. High expression levels of *AGPAT4* may be associated with poor prognosis in cervical and renal cancers, whereas *AGPAT5* is an unfavorable prognostic marker in liver cancer and a favorable one in CRC.

Then PA is converted to diacylglycerol (DAG) by LPIN, a PA phosphatase. Three LPIN isoforms have been described. LPIN1 is upregulated in lung adenocarcinoma tumor tissues, and high LPIN1 expression was correlated with poor prognosis of patients with lung adenocarcinoma (134). In breast cancer, previous results seem to indicate that the high LPIN expression is related to a good prognosis (135). However, in basal-like TNBC, high LPIN1 expression correlates with the poor prognosis of these patients (136). In TCGA dataset analysis, *LPIN2* appears as a favorable prognostic marker in head and neck cancers, while *LPIN3* could be an unfavorable biomarker of endometrial, ovarian, and renal tumors (**Table 1**).

The final step in triacylglycerols synthesis is catalyzed by DGAT, which esterifies the DAG with a FA. Two human DGAT isoforms have been described (182). The expression of DGAT2 in HER2-positive breast cancer was decreased and was closely related to patient prognosis (140). However, data from TCGA reported *DGAT2* as an unfavorable prognostic factor for endometrial cancer (**Table 1**).

Subsequently, TAGs could be stored in LDs, and PLINs, an LD surface family of proteins, are necessary for optimal lipid storage and FA release. There are multiple PLIN proteins encoded by mRNA splice variants of a single PLIN gene. PLIN1 expression in lung adenocarcinoma is associated with apocrine-like features and poor clinical prognosis (137). In contrast, *PLIN1* mRNA expression is significantly downregulated in human breast cancer. The reduced expression of PLIN1 is an independent predictor of OS in estrogen receptor–positive and luminal A-subtype breast cancer patients (138). Also in breast cancer, low expression of PLIN2 was associated with favorable prognosis (139). The prognostic effects of PLINs in several types of cancer from TCGA analysis are multiple and very diverse (**Table 1**).

Eicosanoids are biologically active metabolites of AA and are produced by cyclooxygenases 1 and 2 (COX1 and COX2) [also known as prostaglandin-endoperoxide synthase 1 and 2 (PTGS1 and PTGS2)]. They are overexpressed in a variety of malignant tumors. It has been reported that the mRNA levels of *COX-1* and *COX-2* in lung cancer patients were significantly higher than in normal patients (183). However, another study reports that in tumor cells COX-2 rather than COX-1 expression may account for the variable prostanoid production seen in NSCLC (128). It is clear that multivariate analysis showed that tumoral *COX-2* mRNA expression and lymph node status were the most important independent prognostic predictors for NSCLC survival and disease relapse (129). Elevated COX-2 expression in tumors was significantly associated with lower survival in NSCLC and might be useful in identifying patients who would benefit from additional therapies for managing their disease (130).

The same tendency was observed in CRC, where elevated COX-2 expression, but not that of COX-1, was significantly associated with reduced survival and recognized as an independent prognostic factor (131). However, it has been

reported that COX-1 and COX-2 expression is highly variable in Dukes' C tumors, and changes in COX-1 expression may be of importance in CRC (184).

COX-2 expression level and its prognostic value are also a matter of debate in breast cancer (185). Nevertheless, at least eight immunohistochemical reports have explored expression of COX-2 in a total of 2,392 primary breast carcinomas, of which 40% were found to be COX-2 positive (132). At least, four studies have detected that overexpression of COX-2 is linked to poor prognosis in breast cancer. These studies provide the basis for further estimation of a possible therapeutic effect of COX inhibitors in therapy of breast cancer.

In prostate cancer, a subset of Chinese patients with high-COX-2 expression showed minor disease-free and OS rates than those with low COX-2 expression. In this work, univariate and multivariate analyses suggested that the status of COX-2 protein expression was an independent prognostic factor for patients' survival (133).

Data from TCGA showed *COX-1* and *COX-2* as unfavorable markers of renal cancer, whereas only *COX-1* was a risk biomarker of urothelial cancer (**Table 1**).

Chronic inflammation is a recognized risk factor for CRC, and polymorphisms in genes regulating inflammatory processes appear to modify the risk of neoplasia and the efficacy of non-steroidal anti-inflammatory drugs in CRC chemoprevention. *COX-1* polymorphism G213G was significantly associated with an increased CRC (186). Finally, another study reports four *COX-1* variants that were associated with CRC survival. rs1213266 was associated with approximately 50% lower CRC mortality. Three other variants, including L237M, resulted in significantly elevated CRC mortality risk (187).

Proteins related to FAs transportation are also relevant as cancer biomarkers. Carnitine palmitoyltransferase, CPT1A, is a protein that is responsible for the translocation of FAs from the cytosol to the mitochondrial matrix, where FA oxidation occurs. Associations of shorter disease-free survival with CPT1A positivity in invasive lobular carcinoma of the breast have been found (142).

Another study recognized a gene expression signature composed of 19 genes associated with FAO that was significantly associated with breast cancer patient survival. These 19 genes are referred to as the "fatty acid oxidation (FAO)" signature. Included in this signature were genes that have previously been identified as the core components of the FA β-oxidation pathway, such as *CPT1A*. Moreover, the expression of CPT1A was elevated in estrogen receptor–positive, compared to estrogen receptor–negative tumors and cell lines (143). Data from TCGA clearly confirm a *CPT1A* association with poor prognosis in breast cancer, whereas *CPT1A* is a marker of good prognosis in renal cancer and *CPT1C* in pancreas (**Table 1**).

Other relevant FA transporter is CD36. CD36, a scavenger receptor expressed in multiple cell types, mediates lipid uptake, immunological recognition, inflammation, molecular adhesion, and apoptosis. CD36 has been continually proposed as a prognostic marker in diverse cancers, mostly of epithelial origin (breast, prostate, ovary, and colon) and also for hepatic carcinoma and gliomas (141). Through systematic analysis of the multiple omics data from TCGA, it has been found that the most widely altered lipid metabolism pathways in pan-cancer are FA metabolism, AA metabolism, cholesterol metabolism, and peroxisome proliferator-activated receptor (PPAR) signaling. Genes related to lipid metabolism and immune response that were associated with poor prognosis were discovered including *CD36* (188).

Cholesterol-Related Alterations as Biomarkers of Cancer Prognosis and Survival

First step of cholesterol or mevalonate pathway is catalyzed by acetyl-coenzyme A ACAT1 (**Figure 2**). ACAT1 is a mitochondrial enzyme that catalyzes the reversible formation of acetoacetyl-CoA from two molecules of AcCoA. An increased expression of ACAT1 in intratumor cholesteryl ester–rich breast tumors was reported (189). Also it has been proposed that ACAT1 expression could serve as a potential prognostic marker in prostate cancer, specifically in differentiating indolent and aggressive forms of cancer (144, 145). Data from TCGA suggest that *ACAT1* is a marker of good prognosis in liver and renal tumors. Interestingly, isoform 2 (*ACAT2*) is a marker of good prognosis in CRCs, whereas in endometrial and renal tumors, *ACAT2* has the opposite effect (**Table 1**).

Next step in cholesterol synthesis is mediated by 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS). This enzyme, with two isoforms, condenses AcCoA with acetoacetyl-CoA to form HMG-CoA, which is the substrate for HMG-CoA reductase. *HMGCS2* expression is associated with reduced clinical prognosis and outcomes in patients with CRC and oral squamous cell carcinoma. It has been suggested that HMGCS2 may act as a helpful prognostic marker and essential target for potential therapeutic strategies against advanced cancer (146). Also, it has been described that HMGCS2 works as a tumor suppressor and has a prognostic impact in prostate cancer, capable of predicting the risk of biochemical recurrence (147). However, in TCGA population, both isoforms are favorable makers of renal cancer. Besides, *HMGCS2* determines good prognosis in ovarian and liver cancer (**Table 1**).

HMGCR is the rate-limiting enzyme of the mevalonate pathway (**Figure 2**). HMG-CoA reductase expression in CRC and breast cancer correlates with favorable clinicopathological characteristics and an improved clinical outcome (148–150). Besides, *HMCGR* expression is a predictor of response to tamoxifen in breast cancer (190) and also may predict patient response to radiotherapy in ductal carcinoma *in situ* (191). In TCGA subset, *HMGCR* also is a good prognosis marker of renal tumors (**Table 1**). Statins, lipid-lowering compounds commonly used in cardiovascular disease, are competitive inhibitors of HMGCR. The value of HMGCR as a predictor of response to neoadjuvant or adjuvant statin treatment in cancer was also studied (192).

Once that cholesterol is synthesized, there are several cholesterol transporter proteins that play key roles in cholesterol and phospholipids homeostasis. The ATP-binding cassette transporter ABCA1 is a transmembrane protein responsible

for the reverse cholesterol transport from the inner cell to circulatory system. *ABCA1* is significantly overexpressed in patients of all stages of CRC, and its overexpression gives proliferative advantages together with caveolin-1–dependent increased migratory and invasive capacities (151). Individuals with upregulation of *ABCA1* expression have an improved risk of CRC recurrence and OS independently of tumor stage (8). *ABCA1* also forms part of the metabolic-signature ColoLipidGene able to precisely stratify stage II CRC with 5-fold higher risk of relapse (7). Moreover, the presence of tumoral genetic variants located in *ABCA1* coding region seems to be associated with CRC risk of death (8). In other tumor types, ABCA1 expression was related to positive lymph nodes, but not significantly associated with tumor recurrence or breast cancer–specific survival (193).

Together with ABCA1, ATP-binding cassette G1 (ABCG1) also initiates and propagates cellular cholesterol efflux. Several genetic variants in *ABCG1* have been associated with survival of NSCLC patients (194). Moreover, *ABCG1* expression seems to be a favorable prognostic marker of renal cancer in data from TCGA (**Table 1**).

Other members of the family are the ATP-binding cassettes G4, G5, and G8. High ABCG4 expression has been associated with poor prognosis in NSCLC patients treated with cisplatin-based chemotherapy (152). ABCG5 positivity in tumor buds have been proposed as an indicator of poor prognosis in node-negative CRC patients (153), whereas in TCGA tumors, *ABCG5* seems to have a favorable effect in liver prognosis (**Table 1**).

While cellular cholesterol efflux is mainly performed via ABCA1, cholesterol uptake is principally executed via the LDLR. The prognostic value of LDLR expression was analyzed in CRC where authors found that the absence of LDLR predicts a shorter survival (154). In the same line, lower LDLR expression was an independent prognostic factor associated with longer survival in patients with small cell lung cancer (195). By contrast, TCGA data suggest that *LDLR* could be a bad prognostic marker of pancreatic, renal, and urothelial cancers (**Table 1**).

Lipid-Related Transcription Factor Alterations as Biomarkers of Cancer Prognosis and Survival

Five are the main transcription factors that regulate the expression of mediators of lipid metabolism: SREBP1, SREBP2, PPARγ, NR1H3, and NR1H2. Sterol regulatory element-binding protein 1 (SREBP1) is a known transcription factor of lipogenic genes, which plays important roles in regulating *de novo* lipogenesis. *SREBP1* is overexpressed and strongly associated with worse clinical outcomes in breast cancer (155). Moreover, SREBP1 also seems to have an essential role in pancreatic cancer, regulating tumorigenesis and being associated with bad prognosis (196). However, data from TCGA propose *SREBP1* as a favorable prognostic marker in pancreatic and endometrial cancers (**Table 1**).

The combined expression of sterol regulatory element-binding protein 2 (*SREBP2*) together with *HMGCR*, *NR1H3*, and *NR1H2* genes was associated with poor CRC clinical outcome

TABLE 2 | Preclinical and clinical studies with main drugs evaluated to target the altered lipid metabolism in cancer.

Target	Drug	Type of cancer	Preclinical/clinical trial	
FASN	Cerulenin	Breast Cancer		(48)
		Ovarian Cancer		(201)
	C75	Renal Cancer		(59)
		Breast Cancer		(53)
		Lung Cancer		(43)
	Orlistat	Melanoma		(57, 202)
		Prostate Cancer		(86)
	Fasnall	Breast Cancer		(87)
	C93	NSCLC		(42, 43)
	C247	Breast Cancer		(44)
	TV3166	CRC		(45)
	TVB-2640	NSCLC	NCT03808558	(56)
		TNBC	NCT03179904	(56)
		HG Astrocytoma	NCT03032484	(203)
		Ovarian, Breast Cancer	NCT02223247	(204)
	Triclosan	Breast		(58, 60)
ACLY	SB-204990	NSCLC, Prostate, Ovarian		(51)
		NSCLC		(61)
ACC1/2	ND-630 (GS-0976)	NASH		(71)
	TOFA	HNSCC		(205)
		Ovarian		(33)
	ND-654	HCC		(34)
	GS-0976	NASH		(36)
			NCT02856555	(35)
	ND-646	NSCL		(206)
SCD1	CVT-12	HCC		(207)
	SSI-4	HCC		(208)
	Betulinic acid	CRC		(209)
		GBC		(210)
	MF-438	NSCLC		(211)
	A939572	NSCLC		(212)
		ccRCC		(213)
		Prostate		(213)
CPT1A	Etomoxir	Leukemia		(214)
	Ranolazine	Prostate Cancer		(215)
		Glioblastoma		(216)
	Etomoxir, Ranolazine, Perhexiline	Prostate Cancer		(217)
	Perhexiline	CLL		(218)
		Breast Cancer		(219, 220)
SREBP	Betulin	HCC		(221)
		Melanoma		(222)
	Fatostatin	Prostate		(223, 224)
		Glioma		(225)
		HCC		(226)

(Continued)

TABLE 2 | Continued

Target	Drug	Type of cancer	Preclinical/clinical trial	
LXR	T0901317/GW3965	BPDCN		(227)
	LXR623 and GW3965	Colon/Glioblastoma		(228)
	GW3965	Glioma		(229)
ACAT1	Avasimive	Prostate/Colon Cancer		(230)
		GBM		(231)
		CML		(232)
CD36	FA6.152	Oral Cancer		(80)
		Prostate Cancer		(233)
HMGCR	Fluvastatin	Prostate	NCT01992042	(234)
			NCT00608595	
	Simvastatin	CRC	NCT00994903	(235)
		NSCLC	NCT00452244	(236)
MAGL	URB602	Colon		(237)
PTGS2	Celecoxib	Lung Cancer		(238)
		Ovarian Cancer (HFD)		(239)
		NSCLC	NCT00046839	(+)
		PDAC	NCT01111591	(240)
		Prostate cancer	NCT00073970	(+)
		Early CRC	NCT00608595	(+)
PPARG	VSP-17	Breast Cancer		(241)
FABP4	BMS309403	HCC		(242)
		Prostate Cancer		(243)
	FABP5	SBFI26	CRPC	(244)

(+) Unpublished results.

independent of lymph node metastasis, distant metastasis, and advanced stage (156). Besides, expression of SREBP-2 was elevated in advanced pathologic grade and metastatic prostate cancer and significantly associated with poor clinical outcomes (157).

The PPARγ is a nuclear receptor that controls expression of mediators of lipid metabolism but also the inflammatory response. Additionally, it has been demonstrated that PPAR b/d and a isotypes also have important roles in FAO, FA storage, and cholesterogenesis (197).

Decreased expression of PPARγ has been observed in many tumor types. In this sense, reduced PPARγ expression within the tumor is associated with poor prognosis in lung cancer patients (158, 159). In the same line, tumor expression of PPARγ is independently associated with increased survival of CRC patients (160). Also in patients with breast and prostate cancer, PPARγ is a marker of better prognosis and is associated with better survival (161–163). Importantly, one study reports that cytoplasmic PPARγ expression appeared as an independent marker of poor prognosis in primary breast cancers (198). TCGA analysis proposed PPARγ as a favorable prognostic marker for renal and urothelial cancers (**Table 1**).

Finally, several studies have also evaluated the association between PPARγ genetic variants and the risk of CRC (199).

In patients with stages II/III CRC, polymorphism rs1801282 in PPARγ was significantly associated with tumor recurrence (200).

NR1H3 and *NR1H2* encode for liver X receptor (LXR) α and LXR β, respectively. They are intimately related nuclear receptors that react to elevated levels of intracellular cholesterol by enhancing transcription of genes that control cholesterol efflux and FA biosynthesis. *NR1H3* expression was significantly correlated to better survival in completely resected stages II and III NSCLC patients (164). Moreover, one study reports that *NR1H3* and *NR1H2* belong to a transcription signature associated with poor CRC clinical outcome independent of lymph node metastasis, distant metastasis, and advanced stage (156). This result is validated in TCGA dataset (**Table 1**) where *NR1H2* was also associated with CRC poor prognosis.

TARGETING THE ALTERED LIPID METABOLISM IN CANCER

Because of the essential role of FAs for cancer cell proliferation and progression, drugs to target lipogenic enzymes and/or transcription factors regulating the intracellular lipid homeostasis are considering as promising therapeutic strategies against cancer.

Different drugs have been already evaluated to target (i) lipogenic enzymes (FASN, ACLY, ACC); (ii) the exogenous lipid uptake (LXR, CD36, FABP4/5); (iii) inflammatory signaling pathways (PTGS2); (iv) regulation of intracellular lipid homeostasis (PPARγ, CPT1a, lipin2, HSL, MAGAT, DAGAT…); and/or (v) saturated vs. unsaturated FAs. Their efficacy has been demonstrated in numerous models of cancer, including *in vitro* preclinical and clinical studies.

In **Table 2**, we summarize main drugs evaluated in preclinical and clinical studies. Nevertheless, although the results of these studies are encouraging, side effects due to the many different regulatory mechanisms of lipid metabolism are still a big challenge.

Recently, there is growing interest on complementary approaches by means of dietary interventions for cancer treatment. The success of such interventions requires a deep knowledge of the metabolic requirements of tumors, considering the nutritional status of the individuals—obesity, metabolic syndrome and/or insulin resistance, among others—and the genetic susceptibilities to metabolic alterations. Moreover, the knowledge of the molecular targets and mechanism of action of dietary ingredients will be crucial to apply these approaches with the conventional chemotherapy in order to improve the responses to the clinical treatments and the well-being of patients.

Precision nutrition should be considered at three levels: (1) nutritional guidelines based on age, gender, and other sociocultural factors; (2) individualized recommendations after refined phenotyping; and a (3) genetic-nutrition based on genetic variants with high penetrance and on the response to nutritional interventions (6).

The improvement of the "omics" sciences, including transcriptomics, proteomics, metabolomics, lipidomics, and metagenomics, provides a more complete scenario for

TABLE 3 | Preclinical and clinical studies with bioactive compounds from natural sources to target the altered lipid metabolism and/or associated risk factors (mainly obesity and T2DM) in cancer.

Family	Bioactive compounds	Molecular targets, metabolic effects	Preclinical/clinical trials	References
Polyphenols				
Flavonoids	Gallic acid and its derivatives EGCG, gallate, ethyl gallate, gallocatechin gallate, methyl gallate, propyl gallate, theaflavin-3-gallate	↑AMPK, FAO, thermogenesis		(258)
		↓antiobesity		(259)
		↓Cholesterol, LDL	NCT02147041	(260)
		↓lipogenesis, ↓PPARG, LXR, ↑AMPK		(261, 262)
		↑AMPK, SIRT, PGC1a, FAO, UCP1, CYp7a1		(263)
		↓dyslipidemia		(264)
		↓dyslipidemia	NCT02627898	(265)
		↑FAO, ↓antiobesity	NCT02381145	(266)
		↓HOMAIR, T2DM	Human study	(267)
	Citrus flavonoids			
	Nobilettin	↓HSL, ACC, ↑AMPK, CPT1a, ACOX1, FAO		(268)
	Naringenin	↑PPARα, CPT-1, UCP-2, FAO, ↓SREBP1c, 3HMGCR, hepatic steatosis		(269–272)
	Tangeretin	↑PPARα, FAO		(273)
	Hesperetin	↑PPARα, PPARγ, AMPK, FAO, ↓lipogenesis		(274)
	Baicalin	↓SREBP-1c, FASN, ACC		(275)
	Hispidulin	↑PPARα, CPT1α ↑Acat1, Acad1, HMGCS2		(276, 277)
	Mangiferin	↓inflammation, T2DM, steatosis, ACC, DGAT2, ↑ FAO(CPT1a)		
	Dihydromyricetin	↓hepatic steatosis	ChiCTRTRC12002377	(278)
	Berberin	↓hepatic steatosis, TG and cholesterol levels	NCT00633282	(279)
	Luteolin	↑FAO, ↓lipogenesis, cholesterogenesis, HMGCS1	NCT00633282	(280)
	Quercetin	↓ CYP2E1, inflammation, obesity, T2DM		(281, 282)
Stilbenos	Resveratrol	↓ steatosis, adipogenesis, SREBP1c, lipin1, ACC, ↑AMPK, SIRT1, FAO	(283–285)	
Curcuminoids	Curcumin	↓steatosis, adipogenesis, SREBP1c, FASN, SCD1, GPAT-1, ↑1AMPK, FAO	(286, 287)	
Phenolic acids	Ellagic acid	↓steatosis, Insulin resistance		(288)
Terpenoids				
	Carnosol	↓hyperglycemia, inflammation, lipogenesis, anticancer		(289, 290)
	Betulinic acid	↓SCD, steatosis, lipogenesis		(209)
	Ursolic acid	↑AMPK, FAO, ↓lipogenesis		(291)
	Ginsenoside	↑AMPK, perilipin, FAO		(292–294)
	Licopene	↓inflammation	ISRCTN99660610	(295)

personalized nutritional interventions (13, 245). The main challenge is to define tumor heterogeneities, which can be originated by genomic, epigenomic, transcriptomic, and immune variability. This will lead to patients' stratification for personalized treatments in the clinics (246).

Nutrigenetics aims to study the effect of genetic variants on the dietary response and the risk of several diseases. For example, SNPs in the *CD36* gene associate with dyslipidemia when high amounts of fats are consumed (247). In addition, dietary ingredients affect cancer risk and progression affecting gene expression. Nutrigenomics considers the effect of diet-derived ingredients on gene expression and, consequently, on the proteome and metabolome.

Dietary ingredients and nutrients from natural sources, such as epigallocatechin-3-gallate, curcumin, sulforaphane, and genistein, have been shown to have anticancer properties regulating the expression of genes related to cancer. Polyphenols contribute to the prevention of obesity through the modulation of genes implicated in adipogenesis, lipolysis, and FAO (248–251).

Importantly, in the frame of precision nutrition, dietary interventions might also provide systemic responses affecting the antitumoral response of the immune system, as well as the reduction of low-grade chronic inflammation, dyslipidemia, insulin resistance, and/or obesity.

The direct association of diet with obesity and dysbiosis requires further research to understand the impact of diet on cancer prognosis. High intake of saturated FAs increases the expression of genes related to inflammation, insulin resistance, and/or hepatic steatosis. In contrast, Mediterranean diet downregulates the expression of genes related to oxidative stress, inflammation, and/or insulin signaling (252, 253). Importantly, high levels of triglycerides and LDLs have been associated with CRC prognosis and distant metastasis. Cholesterol in high-fat diets associates with colorectal tumorigenesis (254). Ceramide sphingolipids have been shown to be antitumoral in combination with tamoxifen (255). Phosphatidylcholine is increased in CRC cells. Increased intake of MUFAs is associated with reduce inflammation in CRC cancer (256). Energy-restricted diets supplemented with EPA and α-lipoic acid increase the expression of FAO genes, diminishing the expression of genes related to *de novo* lipogenesis and inflammation (257) (**Table 3**).

Importantly, the efficacy of fasting cycles or cycles of fasting mimicking diets in dampening tumor development has already been established (296), and the implementation of other dietary approaches for cancer therapy is likely to take a similar approach.

CONCLUDING REMARKS

Metabolic alterations of tumors have been well-recognized as one of the hallmarks of cancer. At present, several investigations have demonstrated the consequences of lipid metabolism deregulation in cancer not only sustain tumor growth but also promote cell migration, invasion, and angiogenesis. In this review, we have discussed about the main lipid metabolism alterations found in cancer by describing their mechanism of action and their oncologic implications. Importantly, we emphasize the crucial role of the aberrant lipid metabolism not only affecting the primary tumors but also shaping the tumor microenvironment to promote malignancy and dissemination. Moreover, we have explored the available public data bases containing mRNA data (TCGA) and protein expression data (The Human Protein Atlas) to obtain a global view of the putative implications of lipid metabolism–related genes in cancer prognosis of the most frequent types of cancer according to the WHO: lung, CRC, breast, and prostate cancers.

We also highlight the relevance of "omics" technologies, including genomic and transcriptomic data, considering the phenotypic metabolic status (mainly obesity) to define lipid metabolic scores to be integrated into the clinical advice. Thus, the use of this knowledge will allow a better stratification of patients, which will be translated into improvements on the OS and well-being of the patients. In the frame of precision medicine, new clinical trials integrating classical chemotherapies with precision nutrition–based strategies—bioactive products and diet derived nutrients—will provide an unquestionable line of research in cancer treatment.

AUTHOR CONTRIBUTIONS

LPF and MGC wrote the paper. AR performed the critical revision of the article. All authors conceptually designed the manuscript.

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