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Lipids and cancer: emerging roles in pathogenesis, diagnosis and therapeutic intervention

Lisa Butler[1,2], **Ylenia Perone**[3], **Jonas Dehairs**[4], **Leslie E. Lupien**[5], **Vincent de Laat**[4], **Ali Talebi**[4], **Massimo Loda**[6], **William B. Kinlaw**[7], **Johannes V. Swinnen**[4,*]

[1]Adelaide Medical School and Freemasons' Foundation Centre for Men's Health, University of Adelaide, Adelaide SA 5005, Australia

[2]South Australian Health and Medical Research Institute, Adelaide SA 5000, Australia

[3]Department of Surgery and Cancer, Imperial College London, Imperial Centre for Translational and Experimental Medicine, London UK

[4]Laboratory of Lipid Metabolism and Cancer, KU Leuven Cancer Institute, 3000 Leuven, Belgium

[5]Program in Experimental and Molecular Medicine, Geisel School of Medicine at Dartmouth, 1 Medical Center Drive, Lebanon NH 03756 USA

[6]Pathology and Laboratory Medicine, Weill Cornell Medical College, Cornell University, New York, NY 10065, USA

[7]The Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, 1 Medical Center Drive, Lebanon NH 03756 USA

Abstract

With the advent of effective tools to study lipids, including mass spectrometry-based lipidomics, lipids are emerging as central players in cancer biology. Lipids function as essential building blocks for membranes, serve as fuel to drive energy-demanding processes and play a key role as signaling molecules and as regulators of numerous cellular functions. Not unexpectedly, cancer cells, as well as other cell types in the tumor microenvironment, exploit various ways to acquire lipids and extensively rewire their metabolism as part of a plastic and context-dependent metabolic reprogramming that is driven by both oncogenic and environmental cues. The resulting changes in the fate and composition of lipids help cancer cells to thrive in a changing microenvironment by supporting key oncogenic functions and cancer hallmarks, including cellular energetics, promoting feedforward oncogenic signaling, resisting oxidative and other stresses, regulating intercellular communication and immune responses. Supported by the close connection between altered lipid metabolism and the pathogenic process, specific lipid profiles are emerging as unique disease biomarkers, with diagnostic, prognostic and predictive potential. Multiple pre-clinical studies

*Corresponding author: Johannes V. Swinnen, Laboratory of Lipid Metabolism and Cancer, KU Leuven; Campus Gasthuisberg, ON1 box 812, Herestraat 49, 3000 Leuven, Belgium, j.swinnen@kuleuven.be.

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illustrate the translational promise of exploiting lipid metabolism in cancer, and critically, have shown context dependent actionable vulnerabilities that can be rationally targeted, particularly in combinatorial approaches. Moreover, lipids themselves can be used as membrane disrupting agents or as key components of nanocarriers of various therapeutics. With a number of pre-clinical compounds and strategies that are approaching clinical trials, we are at the doorstep of exploiting a hitherto underappreciated hallmark of cancer and promising target in the oncologist's strategy to combat cancer.

Keywords

Fatty acids; Fatty acid synthesis; Lipid uptake; Lipid droplets; *De novo* lipogenesis; Membrane lipids; Reactive oxygen species; Lipidomics

1 Reprogramming of lipid metabolism as an emerging hallmark of cancer

With more than 17 million new cases per year worldwide and almost 10 million deaths, cancer remains one of the major health issues and societal burdens. According to current concepts, cancer is driven primarily by DNA mutations in genes that promote infinite growth, survival, and metastasis. This typically involves constitutive activation of growth factor receptors and downstream signaling events, but also a rewiring of metabolic processes that provide substrates and energy for cancer cells to thrive in a changing microenvironment [1]. One of the metabolic changes that was first reported almost 100 years ago is the altered usage of glucose. In fact, since the 1920's it has been known that, in contrast to most normal tissues, cancer cells avidly take up glucose and convert it to lactate through the glycolytic pathway irrespective of whether oxygen is present. This phenomenon, known as aerobic glycolysis or the "Warburg effect" underpins modern-day imaging of cancer by FDG-PET. Aerobic glycolysis provides cancer cells with not only energy, but also carbon for the synthesis of cellular building blocks, including nucleotides and lipids [2, 3].

Lipids are a class of water-insoluble metabolites. Estimates of the number of molecular species range from 10,000s to millions [4, 5]. Despite this remarkable heterogeneity most lipids are composed of common building blocks such as fatty acids (FAs) and cholesterol. FAs are aliphatic hydrocarbons with a polar carboxylic headgroup. They differ in the number of carbons and hence acyl chain length and the number and position of double bonds or unsaturations. They are typically classified as saturated (SFA), mono-unsaturated (MUFA) and polyunsaturated FAs (PUFA). FAs are used as building blocks of more complex lipids including phospholipids (PL), which together with cholesterol and sphingolipids are the major constituents of membranes. Phospholipids typically consist of two fatty acyl chains and a polar phosphate head group with choline, ethanolamine, serine or inositol, linked by a glycerol molecule. Sphingolipids, such as sphingomyelins and ceramides, contain a sphingoid backbone instead of glycerol. Di- and triacylglycerides (DAG and TAG) consist of FAs linked to glycerol only. Triacylglycerides, together with cholesteryl esters form lipid stores in intracellular lipid droplets (LDs) and are used as a buffer to keep the cellular lipid composition in balance or as an energy source to drive cellular processes. Many lipids, including diglycerides, ceramides, sphingosines, and

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oxylipins, which are oxidized derivatives of PUFA such as prostaglandins, play important roles as intra- or extracellular signaling molecules [6].

Long before the discovery of DNA mutations as key drivers of the development and progression of cancer, lipids have been implicated in the etiology of this disease. Early studies revealed increased levels of cholesterol in tumor tissues as well as alterations in phospholipids. Studies with radiolabeled substrates as early as the 1960's have brought to light that cancer cells display a dynamic lipid metabolism and actively synthesize and take up lipids [7, 8]. Other early indications for changes in lipid metabolism come from NMR studies of tumors revealing alterations in so called 'mobile lipids' [9]. One of the events that sparked more interest in the association between lipids and cancer is the discovery in the mid-1990s that OA-519, an oncogenic antigen that is highly expressed in human breast cancer (BC), encodes fatty acid synthase (FASN), a key enzyme involved in lipid metabolism [10]. In the meantime, numerous studies identifying differentially expressed proteins and genes, have almost invariably identified lipid metabolism as one of the main affected processes. Together with functional approaches in which specific pathways or enzymes are targeted, a complex picture of metabolic rewiring of lipid metabolism in cancer has emerged. This rewiring is not restricted to the cancer cells themselves, but also implies changes in other cell types in the tumor microenvironment, including stromal and endothelial cells. The full complexity of this rewiring is only just now being uncovered with the advent of more effective technologies to study lipids and lipid metabolic pathways in great detail (see Section 2 of this review).

A number of characteristic changes have emerged that may support cancer cells in a changing microenvironment and that contribute to key oncogenic processes and cancer hallmarks. One key characteristic is that cancer cells are notoriously dependent on a ready supply of FAs and cholesterol (see Section 3). This requirement has been linked to the increased need for membranes to support cell growth and division and provide energy to fuel cellular processes such as metastasis. Whereas most normal cells obtain the bulk of the required lipids from the circulation, cancer cells are known to synthesize a substantial fraction of their lipids *de novo*. Heightened *de novo* lipogenesis mediated through upregulation of the requisite enzymes, is considered a near-universal hallmark of human tumors and their precursor lesions. Nevertheless, cancer cells often do maintain their ability to take up lipids and in a context-dependent manner activate and exploit these mechanisms to acquire lipids from the circulation and adjacent adipose tissue. This provides an interesting link with diet and obesity, which has been supported by numerous epidemiological studies. Diets rich in saturated fat and cholesterol, as well as obesity have been associated with increased risk of many cancers and may lead to increased cancer-related mortality [11–13]. As lipids that are synthesized *de novo* are different in terms of saturation compared to FAs from the circulation, the balance between *de novo* lipogenesis and lipid uptake likely influences the ultimate lipid composition of a tumor.

A large body of evidence now shows that cancer cells also express a repertoire of enzymes that metabolize lipids modulating their lipid content (see Section 4). These processes include FA activation, desaturation and elongation. Depending on the tumor type, a substantial fraction of the lipids is oxidized through the beta-oxidation process, sequestered and stored

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in LDs or secreted or released as vesicles. This extensive rewiring of lipid metabolic pathways appears to be intricately linked to the oncogenic program that is driven by growth factor receptor signaling, as well as other oncogenic events including chromosomal rearrangements, mutations and epigenetic changes, and hormonal stimulation (see Section 5). These signaling pathways in part converge on a few transcriptional regulators that play a central role in lipid metabolism, including Sterol Regulatory Element Binding Proteins (SREBPs), Liver-X-Receptors (LXR) and peroxisome proliferator activated receptors (PPARs). Together with lipid sensors, these factors also play a central role in the adaptive regulation of lipid metabolism by providing the necessary plasticity to adapt to changing microenvironments. Such rewiring of lipid metabolism has long been connected to cell proliferation, cell fate, invasiveness and energy production (see Section 6). Through remodeling of membrane lipids, reprogramming of lipid metabolism also substantially changes the composition and biophysical properties of cellular membranes and affects membrane fluidity and microdomain formation. Evidence is emerging that this membrane lipid remodeling enhances oncogenic signal propagation by generating a feed-forward cycle of oncogenic growth factor signaling [14], in addition to the classical role of lipids as intracellular second messenger generation and membrane protein targeting by lipidation. As lipid metabolism pathways interlink with substrates such as acetyl-CoA and malonyl-CoA that are also used for protein modification, the impact of altered lipid metabolism may extend well beyond classical lipid-regulated pathways and affect numerous cellular processes. Another emerging role is the protection of cancer cells from oxidative and endoplasmic reticulum (ER) stress. In fact, *de novo* lipogenesis and the subsequent relative decrease in poly-unsaturation protects cancer cells from lipid peroxidation caused by reactive oxygen species (ROS) that are abundantly generated in tumors, and guards cancer cells from cell death inducing processes such as ferroptosis that is propagated by lipid peroxidation [15, 16]. FA oxidation may also play a role in this protective mechanism by producing NADH for redox balancing. In addition, LDs have also been implicated in this function and may function as a sink to sequester polyunsaturated FAs or other toxic lipids [17, 18]. Cancer cells are also known to release high amounts of extracellular vesicles, that are largely composed of lipids. This release may help cancer cells to balance their lipid content and moreover appear to function as critical lipid-based transport vesicles involved in intercellular communication [19]. Lipid signaling molecules are released from cells by specific phospholipases such as secreted phospholipase A enzymes (PLAs) and processed to oxidized lipid products or eicosanoids. These lipid-based products are involved in intercellular communication and play an important modulatory role in immune escape and tumor immunology [20].

Reprogramming of lipid metabolism and subsequent changes in lipid profiling can be leveraged for biomarker development. Technological advances enabling simultaneous, quantitative analysis of hundreds of lipids species have revealed the close interconnection between altered lipid metabolism and pathogenic processes. (see Section 7). Characteristic changes in lipid profiles and differential expression of lipid metabolic enzymes in tumor tissues versus non-malignant counterparts have been described as potential cancer biomarkers. Moreover, recent studies have revealed specific lipid signatures that correlate with disease state, prognosis, or therapy response (see Section 7). Alterations in lipid

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profiles form the basis for surgical decision making in intelligent surgical knife applications such as the iKnife [21]. Also in liquid biopsies, such as blood, saliva, sputum and urine samples, changes in lipid profiles have been linked with disease characteristics, including poor prognosis [22–26].

Multiple enzymes involved in lipid metabolism are potential targets for therapy (see Section 8). Several compounds are currently in preclinical and clinical trials. Whilst inhibition of individual enzymes may have limited therapeutic potential due to pathway plasticity, unique context-dependent vulnerabilities have been identified that can be targeted in smart combinatorial approaches. In this context, in view of the protective role of lipid saturation in therapy-induced stress and its involvement in therapy resistance, approaches aiming at increasing poly-unsaturation of lipids in cancer cells bear particular potential [16]. Interestingly, some of these approaches may also target other cell types in the tumor including endothelial cells. Evidence is also growing that lipids play a key modulatory role in immunotherapies, opening new avenues for lipid metabolism-mediated approaches and dietary interventions for immune therapy enhancement. Lipid analogues and lipid-based carriers of therapeutics may also find use in therapeutic approaches (see Section 8).

While we are at the doorstep of witnessing the clinical exploitation of this hallmark in a variety of tumor types, the changes in lipid metabolism known so far most likely present only the tip of the iceberg (see Section 9). Recent advances in analytical approaches, including sophisticated mass spectrometry-based lipidomics applications, mass spectrometry imaging and other spatial approaches have the potential to reveal the hitherto unknown complexity and heterogeneity of lipid metabolic rewiring in cancer and to further establish altered lipid metabolism as a central hallmark in cancer.

2 Profiling of alterations in lipid metabolism in cancer: the coming of age of technology

Although it has long been appreciated that lipids play key roles in cancer, the extent and complexity of the changes in profiles and their roles in cancer and physiology are only now coming to light. Historically, studying lipids has been challenging due to the difficulty in measuring them. In fact, many discoveries of changes in lipid metabolism in cancer have been made through the analysis of data sets other than lipid profiles and the use of other methods that indirectly infer changes in lipid metabolism. A typical example is the immunohistochemical detection of the overexpression of FASN as a surrogate of *de novo* lipogenesis. More recently, many insights into alterations in lipid metabolism have arisen from transcriptome analysis of cancer tissues. A recent Pan-cancer multi-omics analysis of The Cancer Genome Atlas Program (TCGA) datasets recapitulates the enormous complexity of alterations of lipid metabolism pathways in tumors [27]. Affected pathways, at least at the level of the transcriptome, include those involved in FA synthesis, uptake, activation, desaturation, elongation, oxidation and degradation. In addition, the expression of genes involved in the metabolism of more complex lipids including triacylglycerides (TAG), diacylglycerides (DAG), phospholipids (PL), sphingolipids, ceramides, and cholesterol is often altered. Some changes are observed in nearly all explored tumor types, whereas others

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are more cancer-type specific. Genes involved in *de novo* lipogenesis are upregulated in most tumor types. Conversely, genes regulating beta-oxidation appear to be downregulated. Changes in genes related to cholesterol metabolism display a high degree of specificity in different malignancies. Interestingly, the expression of genes involved in arachidonic acid metabolism (phospholipases, cycloxygenases, lipoxygenases) also shows substantial variation among cancer types. *In situ* expression analyses of lipid-related proteins also emphasize the inter- and often also intra-tumor heterogeneity of expression, recapitulating tissue heterogeneity that is characteristic of many tumors. Overexpression of FASN for instance is found in most tumor types, but the degree of expression may vary substantially from tumor to tumor and in many cases correlates with grade and stage of the disease.

Since levels of protein expression do not always correlate with activities, direct lipid analysis is of paramount importance. However, studies of the actual changes in the levels of lipids have long been hampered by the limitation of suitable tools that would allow the quantitative analysis of these molecules. Initial studies applied classical methods such as thin layer chromatography and high-performance liquid chromatography which are limited to the analysis of major lipid classes and phospholipid headgroup classes. Depending on the composition of the mobile phase, polar (phospholipid headgroup classes) or non-polar lipids (cholesterol, triacylglycerides, cholesterol esters) can be separated. Gas chromatography has been instrumental in the analysis of FA composition of lipids, but lacks the ability to analyze intact complex lipids. Further technological advances in lipid measurement and annotation have driven a recent explosion of lipidomic studies reported in experimental model systems of cancer and clinical specimens. As for other macromolecular “omics”, mass spectrometry (MS) plays a central analytical role in lipidomics, coupled predominantly with electrospray ionization (ESI). MS is either performed by direct infusion (known as shotgun lipidomics) or is combined with chromatographic separation techniques (most commonly ultra/high performance liquid chromatography UHPLC) aimed at reducing sample complexity and removing contaminants [28, 29]. Using these techniques, many hundreds of individual lipid species can now be successfully and accurately measured in biological samples, although this still falls short of the putative thousands of lipids present. The gold standard for precise lipid identification and quantification is tandem MS with low energy collision-induced fragmentation and the use of appropriate internal standards. Compared to UHPLC/MS, ultrahigh-performance supercritical fluid chromatography mass spectrometry (UHPSFC/MS) provides advantages in separation of both non-polar and polar lipid classes [30].

Recent developments in high-mass resolution instrumentation including Fournier-transformed MS and MRMS provide unprecedented mass resolution and accuracy. All of the above advances have been markedly assisted by the efforts of the LIPID MAPS consortium to standardize lipid nomenclature, pathway classification and data reporting, as well as generating tools for statistical analysis [31, 32]. Outstanding priorities for further developing lipidomic MS workflows include: improving the accuracy and precision of lipid quantitation through optimization of lipid standards, focus on detection of low-abundance but biologically important lipids, developing more rapid and high-throughput screening platforms, incorporating stable isotope analysis to assess lipid flux, increasing the structural information provided for the acyl chain component of parent lipids, and addressing

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inaccurate lipid identity assignments arising from ionization-inducted artefacts [33, 34]. Further, collaborative guidelines for lipidomic data curation and accurate identification of lipid species are being developed by the Lipidomic Standards Initiative to address common issues of lipid misidentification and data interpretation that have arisen in many published lipidomic studies. Going forward, this focus on standardization will continue to improve the reproducibility of lipidomics studies on a range of platforms, which is essential for precision medicine implementation [35].

Beyond advancements in mass spectrometry instruments, the recent growth in state-of-the-art analytical techniques in the lipidomics field has allowed the detection of very rare lipids and the identification of isometric lipids. A multitude of chemical derivatization protocols have been developed that enable sensitive detection of low abundant lipids. For example, boronic derivatization has been described for the detection of monoacylglycerol [36], the Girard reagent and d_5-GP where successfully used to significantly increase the sensitivity for steroid hormones [37], while for the analysis of oxysterols, derivatization to oximes, Girard hydrazones and picolinyl or nicotinyl esters has been described (reviewed in [38]). Resolution of glucosylceramide and galactosylceramides isomers has been demonstrated with a HILIC based LC method and has revealed a remarkable isomeric preference of these lipids in different tissues [39]. Several methods have been described that allow the detection of C=C location isomers such as ozone-induced dissociation (OzID) [40] and high resolution ion mobility-mass spectrometry [41]. A recently published study demonstrated a large scale analysis of C=C location by combining the C=C specific Paternò–Büchi derivatization with LC-MS/MS and revealed that ratios of C=C isomers show much less interpersonal variability than their individual abundances [42]. By using a click-chemistry based alkyne labeling of lipids Thiele and colleagues were able to reach subfemtomole levels of sensitivity in detecting fatty acid incorporation into phospholipids and neutral lipids. In addition, they demonstrated that this technique can be applied at the single cell level [43].

Lipidomic analyses have been performed in a wide range of cancer and non-malignant cell lines and well as in clinical tissue specimens. These studies confirmed the extensive nature of lipid changes in many tumor types. In our own analysis, for instance, we discovered 91 differentially expressed phospholipid species in tumor versus non-malignant tissue homogenates from non-small cell lung cancer patients [44]. A major issue of all ‘omics’ approaches that utilize homogenized tissue samples is the loss of spatial information and the change in cellular tissue composition as a confounding factor. This is particularly critical in the context of heterogeneous and multifocal solid tumors containing multiple cell types including immune cell infiltrates. These appear to have a unique and potentially targetable lipid signature (reviewed in [45]). The advent of MS imaging (MSI) provided the opportunity to visualize lipid abundance in histological sections of tumors or needle biopsies, and relate the MS data to pathological features of the tissue [46–48]. MSI acquires mass spectra from material ablated from tissue sections using either a laser, particle beam or solvent spray. The x-, y- coordinates of each data point are recorded, and the spatial and mass spectral data can be used to build up a distribution map of a molecular ion of choice [49–51] containing spatial distributions and relative abundances of the sample ions. Importantly, the resultant lipid-ion image can be correlated with histological features of the tissue section [52]. Matrix-assisted laser desorption/ionization (MALDI) was introduced in

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the late 1980's as a soft ionization technique for label-free MS analysis of large biomolecules. It has subsequently been developed into an imaging technology [53–55], applied to metabolomics and lipidomics in solid tissues [56–58]. More recently, desorption electrospray ionization (DESI) MSI, which uses a charged solvent rather than a laser for ionization, has allowed direct lipid analysis in tissues under ambient conditions with minimal pre-treatment. Notwithstanding the substantial progress that has been made in the field of MSI of lipids, a number of outstanding issues remain to be addressed [59]. These include the scope of evaluation of the lipidome produced and the overall quantitative capacity of lipid MSI-maps. One of the most important limitations of MALDI-MSI is the fact that it detects fewer lipid species than ESI-LC-MS, which may reflect ion suppression by highly abundant lipid species, uncontrolled in-source decay (ISD), specific matrix requirements for successful MSI and/or the ambiguity of some lipid species with respect to mass [52].

Taken together, the analysis of lipid metabolism pathways through various methods has revealed a complex rewiring in tumor tissue that is heterogeneous and that extends beyond the tumor cell compartment. Despite this heterogeneity, a number of characteristic and recurrent changes are emerging that we highlight in the next sections of this review.

3 Acquisition of lipids by cancer cells: the Yin and Yang of *de novo* lipogenesis versus exogenous lipid uptake

One of the earliest and best studied aspects of lipid metabolism in cancer is the notorious dependence of cancer cells on a supply of FAs and other lipids. This trait has been linked to the increased need of cancer cells to acquire lipids for membrane synthesis and energy production required for rapid cell proliferation. Generally, there are two main sources of lipids for mammalian cells: exogenously-derived (dietary) lipids and endogenously-synthesized lipids (Figure 1).

In normal physiology, most lipids are derived from the diet. Dietary lipids are taken up by intestinal cells and packaged into chylomicrons (CMs), which are short-lived lipoprotein particles that enter the bloodstream and deliver FAs for oxidation in heart and skeletal muscle, and for storage in adipose tissue. The liver secretes a second type of TAG-rich lipoprotein particle, very low-density lipoproteins (VLDLs), which are much longer-lived in the bloodstream and serve to redistribute TAGs to peripheral tissues [60]. CMs and VLDLs are spherical particles that contain a core of neutral lipids, mainly TAGs. The surface of these particles contains polar lipids, including phospholipids, free cholesterol, and several exchangeable apolipoproteins [61]. Apolipoproteins can act as ligands for cell surface receptors enabling lipid uptake through receptor-mediated endocytosis mechanisms. They also function as cofactors for lipases, such as lipoprotein lipase (LPL), which is tethered to the luminal surface of capillary beds that perfuse LPL-secreting tissues and releases free fatty acids (FFA) from the complex lipids in lipoprotein particles [62]. FFA, but also more complex lipids, such as phospholipids, can be taken up by cells through both passive and active uptake mechanisms. One of the best studied mechanisms involves the FA translocase 'Cluster of Differentiation 36' or CD36. Other mechanisms involve FA transport proteins

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(FATPs)/SLC27A, and fatty acid binding proteins (FABPs). The remaining intermediate-density and low-density lipoproteins (IDL and LDL) are cholesterol-rich and are also taken up by specific receptors on the surface of cells, such as the LDL receptor (LDLR), providing cholesterol required for membrane formation or more specialized functions such as steroid or bile acid synthesis [63]. Recent evidence indicates that cells can also acquire lipids from circulating or locally produced extracellular vesicles which are taken up by endocytosis or membrane fusion (reviewed in [19]).

The second source of lipids is *de novo* lipogenesis, primarily from pyruvate, the end-product of glycolysis, and from glutamine [64]. The initial step in FA synthesis is the export of citrate from the mitochondrion to the cytosol. Three cytosolic enzymes then act sequentially to produce palmitic acid. ATP citrate lyase (ACLY) cleaves cytosolic citrate to yield acetyl-coenzyme A (acetyl-CoA), the basic building block for cholesterol through the mevalonate pathway and for FA and more complex lipids. Acetyl-CoA carboxylase-α (ACACA) catalyzes the carboxylation of the 2-carbon acetyl-CoA substrate to yield the 3-carbon product, malonyl-CoA, which forms the nidus for subsequent elongation by FASN, the core enzyme of FA synthesis. The direct product is palmitic acid, a fully saturated FA of 16 carbons, which can be further elongated by elongases (ELOVLs) and desaturated by stearoyl-CoA desaturases (SCDs), which introduce a double bond at the Δ9 position of palmitoyl-(16:0) or stearoyl-CoA (18:0) to generate the monounsaturated FAs [65–67]. The resulting FAs are used as substrates for synthesis of TAG, cholesterol esters, and plasma membrane phospholipids. In adult humans, *de novo* FA synthesis is restricted mainly to the liver, adipose tissue, and lactating mammary gland [68], and is considered to be of minor importance, owing to sufficient levels of dietary fat and the preferential use of these circulating lipids for structural synthesis [69]. This principle has been demonstrated in a variety of mouse models with tissue-specific knockout of FASN expression resulting in no detectable phenotype under non-stress conditions [70]. Studies have additionally shown that normal tissues (often compared to adjacent tumor tissue) rarely express significant amounts of FASN protein [71–75].

3.1 De novo lipogenesis in cancer cells: the lipogenic phenotype

In contrast to normal cells, most cancerous cells actively synthesize lipids such as FAs and cholesterol. Early studies using radioactivity-based methods to measure lipid synthesis showed that *de novo* FA synthesis accounts for 93% of the total cellular lipid content in certain cancer cell types [76]. FASN overexpression has been reported in a wide variety of human solid tumors [77]. Depending on the tumor type and on staining and scoring methods, overexpression has been observed in 15 to 95% of samples, often with inter- and intratumoral heterogeneity. Although this overexpression has been commonly linked to the increased need for membrane production required for rapid cell division, in several tumor types overexpression can be observed in precancerous lesions, as well as in invasive low-grade tumors like prostate cancer, where proliferation is limited. Indeed, synthesis of lipids is essential not only to form new cellular membrane during cell division, but also for the post-translational modification of signaling molecules, as well as for energy storage [78] (see also Section 6). FASN has been shown to facilitate oncogenesis when overexpressed in the mouse prostate [79] and has been proposed as a candidate oncogene [79–89]. Elevated

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levels of FASN were found in transgenic cancer models and its levels increased with the age, tumor progression and metastasis [90]. In prostate cancer, FASN is overexpressed especially in the metastatic, castration-resistant setting [89, 91–94] and is associated with poor prognosis [93, 94]. *FASN* inhibition with siRNA in LNCaP prostate cancer cells blocks cell proliferation and reduces pseudopodia and invadopodia formation, cell adhesion, migration and invasion [95–97].

The other lipogenic enzymes (ACLY and ACACA) are also overexpressed or activated as a near-universal metabolic feature of cancer [69, 98]. Blockade of these enzymes using RNA interference or chemical inhibitors reduces cell proliferation and evokes cell death in many cell line models and attenuates tumor growth *in vivo* [98–100]. Some of these studies, however, have to be interpreted with caution. In earlier studies promiscuous inhibitors such as cerulenin or TOFA were used, siRNAs were administered at high concentrations resulting in substantial off-target and nonspecific antiproliferative effects, and in many cases, cells were cultured with low levels of exogenous lipids, forcing them to depend on endogenous synthesis. Part of the growth inhibiting effects of lipogenesis inhibition may also be mediated by the accumulation of intermediates such as malonyl-CoA and subsequent protein modification as has been reported in endothelial cells [101]. More recently, it has been shown that suppression of *de novo* lipogenesis is the mechanism responsible for AMPK-mediated growth inhibition of prostate cancer growth, suggesting AMPK as a therapeutic target [102]. Finally, selective FASN inhibition with a potent, specific and irreversible inhibitor results in decreased growth of castration-resistant prostate cancer with downregulation of both full-length AR (AR-FL) and its ligand-independent splice variant [103].

Cancer cells also often show upregulation of enzymes involved in the synthesis of cholesterol, although this phenomenon appears to be more tumor-type specific. Blockage of cholesterol synthesis using inhibitors of HMG-CoA reductase (the rate-limiting enzyme of cholesterol synthesis) or of other downstream enzymes such as squalene synthase (farnesyl-diphosphate farnesyl transferase) reduces cell proliferation. Notably, the use of statins (inhibitors of HMG-CoA reductase) has been associated with a reduced risk of cancer development in large epidemiological studies, supporting a role for cholesterol synthesis in the development of cancer, although some controversy exists [104–107].

Cancer cells also show changes in the pathways that provide the building blocks for lipid synthesis. Besides the well-known Warburg-related increase in glucose uptake and glycolysis that is seen in many tumor types, cancer cells additionally rely on glutamine and acetate as carbon sources for lipid biosynthesis, particularly when access to glucose-derived acetyl-CoA is impaired [108–111] because pyruvate entry into the mitochondrion is curtailed as a manifestation of the Warburg Effect [112]. Under conditions of actual or pseudo-hypoxia or defective mitochondria, glutamine-derived α-ketoglutarate may be converted to citrate through reductive carboxylation and thereby contribute to *de novo* lipogenesis [113–117]. In cancer cells, acetyl-CoA can additionally be supplied via the ligation of acetate and CoA by acetyl-CoA synthetase (ACSS) in the cytoplasm [116, 118–122]. Interference with this enzyme can also block BC cell proliferation [120]. Recent evidence indicates that cancer cells can also use fructose as a source to produce FAs and

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more complex lipids [123], and the fructose transporter GLUT5 is induced by hypoxia [123, 124]. Overall, these findings support the importance of lipid synthesis for cancer cells and illustrate remarkable adaptability in the use of substrates for lipid production.

3.2 Lipid uptake by cancer cells

Despite the strong evidence for *de novo* lipogenesis as an important source of lipids for cancer cells, there is also solid body of evidence showing that exogenous lipid uptake remains an important route of lipid acquisition for many cancer cells. As early as the 1960's pioneering work by Spector showed that FFA contained in the ascites fluid of Ehrlich ascites tumors could be esterified and catabolized by the tumor cells [125]. Almost a half century later, Louie et al. mapped palmitic acid incorporation into complex lipids, highlighting the ability of cancer cells to use exogenous FAs to generate lipids required for proliferation and oncogenic signaling [126]. Numerous studies over the past decade have supported the role of lipid uptake as an important route for lipid supply. One of the mechanisms that has been firmly established implies a critical role for LPL. LPL was found to be overexpressed in several tumor types including hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and BC (see also Section 5). In chronic lymphocytic leukemia LPL was identified as one of the most differentially expressed genes [127] and as an independent predictor of reduced survival [128–133]. In hepatocellular carcinoma, high levels of LPL correlate with an aggressive tumor phenotype and shorter patient survival, supporting LPL expression as an independent prognostic factor [134]. Kuemmerle and colleagues showed that nearly all breast tumor tissues express LPL and that LPL-mediated uptake of TAG-rich lipoproteins accelerates cancer cell proliferation [135]. LPL is significantly upregulated in basal-like triple-negative breast cancer (TNBC) cell lines and tumors [135–137], most particularly in claudin-low TNBC [138, 139]. LPL and phospholipid transfer protein (PLTP) are upregulated in glioblastoma multiforme (GBM) compared to lower grade tumors, and are significantly associated with pathological grade as well as shortened survival of patients. Knockdown of LPL or related proteins [140] or culturing cancer cells in lipoprotein-depleted medium has been shown to result in significantly reduced cell proliferation and increased apoptosis in several cancer cell types [191]. Importantly, LPL may be produced locally or may be acquired from exogenous sources, such as human plasma or fetal bovine serum [141]. Besides the classical role of LPL in the release of FA from lipoprotein particles, recent work by Lupien and colleagues found that LPL-expressing BC cells display the enzyme on the cell surface, bound to a specific heparan sulfate proteoglycan (HSPG) motif. The failure to secrete LPL in this setting may arise from a lack of expression of heparanase, the enzyme required for secretion by non-cancer tissues. Cell surface LPL grossly enhanced binding of VLDL particles, which were then internalized by receptor-mediated endocytosis, using the VLDL receptor (VLDLR). Hydrolytic activity of LPL is not required for this process, and interestingly, BC cells that do not express the LPL gene do express the requisite HSPG motif and use it as "bait" to capture LPL secreted by other cells in the microenvironment. This was the first report of this nonenzymatic role for LPL in cancer cells, although elegant work by Menard and coworkers has shown brisk HSPG-dependent lipoprotein uptake by GBM cells that was upregulated by hypoxia [142]. This high capacity LPL-dependent mechanism for lipid acquisition appears to be of greater importance to certain BC cell lines *in vitro* than others, supporting previous descriptions of distinct

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metabolic features of different BC subtypes. In GBM there is also evidence [143] that LPL is secreted, captured by glycosylphosphatidylinositol high density lipoprotein binding protein 1 (GPIHBP1) rather than a HSPG, on the antiluminal aspect of the capillary endothelial cell, and shuttled to the inner capillary surface to create a “platform for lipolysis”. GPIHBP1 is present in glioblastoma tumor capillaries and, with LPL, facilitates the processing of TAG-rich lipoproteins [144]. Based on this and other work, it appears that cancer cells may employ LPL for both extracellular hydrolysis of TAG carried in lipoproteins as well as bulk lipoprotein endocytosis. Various other lipases, including endothelial lipase [145–149], and monoacylglycerol lipase [126, 144, 150–153], have been implicated in these mechanisms, as well as lipoprotein receptors.

A role for CD36 in FFA uptake has been well established in several cancer types. CD36 is markedly upregulated in various tumor types including BC [135], GBM, gastric cancer [154], oral squamous cell carcinoma and ovarian cancer [155]. CD36 knockdown in BC cells abolished the capacity of FFA to stimulate proliferation [156]. Inhibition of CD36 in mouse models of BC grossly reduced metastasis, diminished the ability of a high fat diet to stimulate tumor growth [157] and impaired the growth of anti-Her2 therapy-resistant tumors in a mouse model of Her2+ BC. [158]. Prostate cancer is known to be highly lipogenic, and CD36 was found to play an important role in FA uptake and its deletion attenuated cancer progression [159]. CD36-mediated FFA uptake has been linked the epithelial to mesenchymal transition in hepatocellular carcinoma [160] and with metastasizing potential in several cancer types [157]. CD36 is also induced in therapy-resistant melanoma [161]. Taken together, this recent body of work establishes the uptake of FFA via CD36 as a significant mechanism for lipid acquisition by cancer cells. Besides CD36, the uptake of FAs is facilitated through the upregulation of fatty-acid-binding proteins 3 and 7 [162].

3.3 Lipid droplets as intracellular reservoirs of lipids: the lipid-accumulating phenotype

In several studies, lipid uptake and synthesis have been linked to the formation of LDs, which mainly consist of TAG and cholesterol esters and represent a third reservoir and source of lipids for cancer cells, particularly under stress conditions such as hypoxia. Increased abundance of LDs is a feature of many aggressive cancers [163–166]. This “lipid accumulating” phenotype, may enable cells to make use of lipid stores in conditions of stress or limiting access to lipids. The role of LDs, however, extends far beyond a reservoir function as is further discussed in Section 4.8 of this review.

3.4 Exploiting fat stores, associations with obesity and high fat diets

Interestingly, several tumor types exist in anatomic proximity to adipose cells, including primary BCs in the mammary fat pad, metastatic ovarian carcinomas that “home” to omental fat, prostate tumors adjacent to the peri-prostatic fat and a variety of metastases in fatty bone marrow [167]. Recent work has uncovered the ability of cancer cells to exploit the large quantity of fat stored in tumor-adjacent adipocytes. Traditionally considered an inert tissue whose sole function was energy storage, white adipose is now appreciated as an important endocrine and metabolic organ, as well as a key player in immunity and inflammation [168]. During early tumor invasion, BC cells enter the mammary fat pad [114]. Studies have shown that interaction with adipocytes augments the growth and survival of breast and other types

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of tumors. BC cells secrete a variety of factors, including cytokines and lipolytic enzymes that directly affect adipocytes. Reciprocally, tumor-associated adipocytes secrete adipokines, growth factors, proteases, and FAs that enhance tumor growth and survival [169–171]. The lipolysis of TAG stored in the lipid droplets of adipose tissue and subsequent release of FFA increases tumor growth and results in the reduction of adipose tissue mass observed in the BC microenvironment [172]. Adipocyte-derived FAs promote BC cell proliferation and triglyceride accumulation [169, 173]. Several studies have shown that BC cells increase exogenous FA uptake and utilization from adipocytes by upregulating genes involved in FA uptake, including FABP4 and CD36 [173–176].

3.5 Plasticity in lipid acquisition

Many tumor types show evidence for the activation of both lipid synthesis and uptake, either simultaneously or in a plastic, cell type- and context-dependent manner. Hepatocellular carcinoma for instance has been found to be both lipogenic and lipolytic. Similarly, BC cells can show both phenotypes, although the balance between the lipid acquisition modes appear to be subtype-dependent [137]. TNBC appears to be more dependent on the uptake and storage of exogenous lipids than estrogen receptor-positive BC, which differentially rely on FA synthesis, mobilization, and oxidation. In prostate cancer both lipid synthesis and uptake are increased, and are induced by androgen signaling [177]. Interestingly, many cancer cells seem to be able to adjust their reliance on *de novo* lipogenesis vs. lipid uptake both in response to exogenous nutrient availability and the functional status of cellular FA synthetic machinery. Several groups have now shown that prolonged incubation of cancer cells in lipoprotein-depleted media can elicit a significant upregulation of genes involved in *de novo* lipogenesis, FA or lipoprotein uptake, and cholesterol synthesis [15, 178, 179]. Studies have highlighted the upregulation of FA uptake channels [116, 157, 175, 176] and lipolytic enzymes, including monoacylglycerol lipase [144, 150, 151], endothelial lipase [145, 146], and LPL [135, 179] in a variety of tumor types. Moreover, several reports have shown that the cytotoxic effects of inhibiting *de novo* lipogenesis *in vitro* may be partially averted by supplying cancer cells with exogenous lipid [72, 98, 134, 135, 142, 180–182]. Other stress conditions may also affect the balance between liquid acquisition pathways. GBM cells for instance under hypoxic and acidic stress acquire a lipid droplet-loaded phenotype characterized by increased recruitment of all major lipoproteins (HDL, LDL and VLDL). Here, stress-mediated uptake of lipoproteins was shown to be mediated through heparan sulfate proteoglycan-dependent endocytosis (involving lipoprotein receptors VLDLR and SR-B1) [183], similar to the findings in BC [179]. Metabolic plasticity has also been observed upon exposure of cancer cells to adipose cells. BC cells for instance induced a lipolytic phenotype when co-cultured with adipocytes, and adjusted their metabolism to capitalize on the influx of FFA [169]. Metabolic plasticity in the context of the cancer cell-adipocyte interaction was further highlighted by the finding that prostate cancer cells cocultured with adipocytes enhance the expression of genes related to FA uptake and transport, including CD36 [167, 184]. Importantly, adipocytes “preloaded” with triglyceride using a high-fat diet accelerated the growth of bony prostate cancer xenografts in that study. Together, these observations support a model in which cancer cells adapt their metabolism in response to the availability of lipids in the microenvironment, including from the circulation and adjacent adipocytes, to support growth [171, 179, 185].

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Interestingly, alterations in the balance between lipid uptake and synthesis have also been found in other cell types in the tumor microenvironment. In endothelial cells in tumor microvessels, CD36 expression is overall downregulated. Tumor-associated endothelial cells have been shown to rely on FA-derived carbon for DNA synthesis [186]. CD36 was also shown to be low in tumor-associated stroma and to be associated with tumor aggressiveness [187]. Significant upregulation of *de novo* lipogenesis has also been found to be essential for the differentiation of monocytes into macrophages. Upon stimulation with macrophage colony-stimulating factor, SREBP-1c driven upregulation of FASN, ELOVL6 and SCD leads to dramatic shift towards the synthesis of saturated and mono-unsaturated FAs. Moreover, knock-down of FASN was detrimental to macrophage's ability to develop filopodia [188].

3.6 Consequences of lipid acquisition pathways for cellular lipid composition

Critically, the choice between synthesis vs. uptake pathways dramatically affects the lipid composition of membranes with important consequences for membrane and cancer cell biology. In fact, as mentioned before, *de novo* FA synthesis produces saturated and mono-unsaturated FAs as humans lack delta-12 and delta-15 desaturases required to produce PUFA. As a consequence, mammals cannot generate FAs that are unsaturated in the ω−3 or ω−6 position of the acyl chain. Hence, these essential FAs (α-linoleic acid and linoleic acid) must be obtained from the diet [67]. Lipidomics analysis in fact has demonstrated that a switch between FA synthesis and uptake dramatically affects the degree of lipid unsaturation in cancer cells and that this has major consequences for cancer cell biology (see Section 6).

4 Metabolism and fate of lipids in cancer cells

Concordant with the vast diversity of lipids and the many roles they play in cell biology, FAs and other lipid building blocks are extensively metabolized in diverse pathways leading to the synthesis of more complex lipids including PLs, TAGs or oxylipins, just to name a few, which play diverse roles ranging from membrane formation, lipid storage and cell signaling. Lipids are also an important source of fuel for energy production. Intriguingly, most of these pathways and enzymes are affected in cancer cells, illustrating the extent of the rewiring of lipid metabolism in cancer and the central role lipids play in cancer biology.

4.1 Activation of lipids

For FAs to be used in metabolic pathways (both anabolic and catabolic) they need to be activated by conversion to fatty acyl-CoAs. This is a process that is catalyzed by long chain Acyl-CoA Synthetases (ACSLs). In humans there are 5 ACSL isoforms, each of which has a different cellular and subcellular distribution, regulation, substrate specificity, and enzyme kinetics. Cumulative evidence from several studies indicates that nearly all members are dysregulated in cancer, depending on the tumor type. The strongest evidence for a role in cancer development and progression is available for ACSL1 and ACSL4. ACSL1 is found to be overexpressed in multiple types of cancer, including breast, myeloma, liver and colon [189–191]. In some cases, such as colon, overexpression of ACSL1 is correlated with a poor prognosis and is thought to play an oncogenic role. In lung squamous cell carcinoma, however, the expression is downregulated, suggesting a context-dependent tumor suppressing role [192]. Similarly, ACSL4 is upregulated in many cancers, including cancer

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of the liver, prostate, breast and colon, but is downregulated in gastric cancer. Interestingly, recent evidence indicates that ACSL4 is essential in the induction of ferroptosis, a form of regulated cell death propagated by toxic lipid peroxides [192]. Induction of ferroptotic cell death may represent a therapeutic strategy against various types of cancer with high levels of ACSL4 (see Section 8).

4.2 Intracellular transport of lipids

FAs serve several functions in the cell. They are extensively metabolized and used as an energy source or as building blocks to generate more complex derivatives. These processes may take place in different compartments of the cell, such as the endoplasmic reticulum, Golgi apparatus, peroxisomes or mitochondria. This requires an intensive transport of lipids that is mediated by a superfamily of lipid-binding proteins, including Fatty Acid Binding Proteins (FABPs). FABPs act as lipid chaperones that bind saturated and unsaturated FAs and other hydrophobic ligands such as eicosanoids, and monoacylglycerols. FABPs form a family of 12 members that exhibit unique patterns of tissue expression. Numerous reports mention changes in the expression of FABPs in various cancer types. FABP1 (also known as liver type FABP) is overexpressed in many tumor types while FABP4 (or adipocyte FABP) has been described as a tumor suppressor that correlates with tumor stage and is often downregulated in prostate and bladder cancer [193]. In the serum, on the other hand, FABP4 levels have been reported to be higher in patients with cancer, such as BC, than in healthy controls [194]. High extracellular FABP4 is correlated with tumor size and lymph node involvement. It is reported to promote metastasis of prostate cancer and is a risk factor for BC, linked with obesity [194]. FABP-4 interacts with hormone-sensitive lipase (HSL) and modulates several signaling pathways that regulate inflammatory responses mediated by JNK/inhibitor of kappa kinase (IKK) [195]. FABP5, or epidermal FABP, is also upregulated in many cancer types, including colon, pancreatic, endometrial, and gastric cancer, cancer of the bladder, skin, prostate, head and neck, hepatocellular carcinoma, and non-small cell lung cancer [193]. FABP5 has been shown to deliver ligands to PPAR-β/δ in the nucleus (see Section 5) and to increase angiogenesis through the PPAR-γ-VEGF signal transduction [193]. Knockdown of FABP5 inhibits cell proliferation, invasion and metastasis in several preclinical cancer models. Hepatocellular carcinoma patients with overexpressed FABP5 have a worse progression and higher relapse rates [196]. FABP6 or ileal bile acid binding protein (I-BABP), like FABP4, is mainly expressed in adipocytes and macrophages and is thought to be involved in the link between bile acids and colon cancer. FABP7, or Brain FABP (BFABP) expression is increased in renal cell carcinoma and in well- and moderately differentiated prostate cancer (Grade groups 1–3) and is down-regulated in poorly differentiated tumors (Grade groups 4–5) [197]. High expression was associated with proliferation and tumor size of melanoma biopsies and was shown to promote proliferation and invasion in melanoma cells [198]. Also FA binding protein 9 (FABP9), or Testis-FABP (T-FABP) is overexpressed in prostate cancer and is thought to play an important role in progression and development of prostate cancer [199].

4.3 Desaturation of lipids

FA desaturation is a process almost ubiquitously activated in tumors. Desaturation, or introduction of one or more double bonds, into FAs is catalyzed by a family of FA

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desaturases, which vary based on their substrate preferences. Stearoyl-CoA desaturases (SCD), for example, introduce a double bond at the cis-delta-9 position of saturated fatty acyl-CoAs, thereby converting stearoyl-CoA or palmitoyl-CoA to oleate or palmitoleate, respectively. Two human isoforms of SCD exist, SCD1 and SCD5, representing the final enzymes involved in the *de novo* FA synthetic pathway. FA desaturases, on the other hand (FADS1–3), primarily generate PUFAs from the dietary essential fatty acids, linoleic acid (LA, 18:2*n*-6) and α-linolenic acid (ALA, 18:3*n*-3). SCD1 is most widely expressed in human cells and is overexpressed in many tumors [200–202]. It has been reported that rapidly proliferating cancer cells have a greater demand for MUFAs, which are utilized mainly for the synthesis of membrane PLs and TAGs, and indeed most cancer cells are characterized by a higher relative proportion of MUFAs than corresponding normal tissues [203], a notable exception being colorectal cancer which is enriched in PUFA according to recent reports [204, 205]. Knockdown or chemical inhibition of SCD1 show promising efficacy and treatment sensitization in a range of cancers [206–209]. Although the underlying mechanism remains to be fully explored, interference with SCD1 in lipogenic cancer cells has been shown to disturb the balance between saturated and monounsaturated FAs, and leads to ER stress and changes in cardiolipins. As a result, cytochrome c release drives cells into apoptosis [210]. FA desaturation requires strong reducing equivalents and oxygen, which can be particularly challenging in the hypoxic conditions experienced particularly in solid tumors. However, tumors have developed approaches to overcome these limitations and maintain membrane desaturation. For example, in glioma models, the SREBP-dependent lipogenic program (see Section 5) and SCD are more highly expressed in hypoxia, and this is in part shown to compensate for the reduced oxygen availability [211]. In renal cell carcinoma models, TAGs provide a reservoir for MUFAs and are preferentially shunted to lipid droplets; the MUFAs can be subsequently hydrolyzed and assembled into phospholipids under hypoxic conditions [212].

Although far less-studied, the delta-6 desaturase FADS2 is also overexpressed/overactive in certain cancers [213–215] and can function as a compensatory pathway, which can generate the unusual FA sapienate rather than palmitoleate from palmitate, to bypass the cells' reliance on SCDs for MUFA production [216]. Inhibition of one or both FADS enzymes has shown preclinical efficacy in intestinal cancer [217]. Given their respective roles in generation of MUFAs and PUFAs, it is likely that the balance between these two families of desaturases has a profound impact on membrane properties and therapy response/resistance of cancer cells. Membrane unsaturation mediated by SCD/FADS or the uptake of extracellular MUFAs/PUFAs markedly enhances the fluidity of cellular membranes, however PUFAs in particular are highly oxidizable and therefore make cells more susceptible to ferroptosis, an iron-dependent form of cell death induced by lipid peroxidation. Synthesis or uptake of MUFAs provides a robust protection from ferroptosis [218], however whether this is due solely to the relative depletion of membrane PUFA or includes multiple other mechanisms remains unclear (see also Section 6).

4.4 Elongation of lipids

Several studies show that membrane lipid elongation is a common feature in cancer when compared to matched normal tissue. Lipid elongation is catalyzed by a class of enzymes

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called elongases (ELOngation of Very Long fatty acids; ELOVLs), comprising 7 members (ELOVL 1–7). ELOVLs are key components of the elongation system that adds two carbon units to the carboxyl end of fatty acyl chains. While their precise specificities are not fully characterized, ELOVL1, 3 and 6 elongate saturated FAs and MUFAs, ELOVL2 and 4 elongate PUFAs, ELOVL5 elongates MUFAs and PUFAs, and ELOVL7 elongates saturated FAs and PUFAs [219, 220]. As targeting ELOVLs has revealed functional effects in cancer models [221–223], it is likely that membrane lipid elongation is more than just a consequence of enhanced *de novo* lipogenesis in cancer. In prostate cancer, knockdown of ELOVL7 has been shown to reduce saturated FAs in membrane phospholipids but also the levels of neutral lipids such as cholesterol, which in turn reduced synthesis of the androgen that drive prostate cancer growth [223]. A study in glioma models provides further mechanistic insights, where ELOVL2 alters membrane long-chain PUFAs in order to promote epidermal growth factor receptor (EGFR) signaling through membrane domains [224]. In addition to the role of ELOVLs in membrane lipid elongation, through the production of arachidonic acid, PUFA elongation via ELOVL2 and ELOVL5 is necessary for the generation of inflammatory and signaling lipids, many of which have potent signaling effects in cancer and on immune cells. Moreover, elongation generates NAD+ and may therefore contribute to sustaining glycolysis, a process analogous to the desaturation of FAs or lactate fermentation [225].

4.5 Hydroxylation of lipids

Hydroxylation of FAs is a process whereby a hydroxyl group is introduced in the fatty acyl chain and occurs naturally in microbial, plant and mammalian cells. Hydroxylation of FA in mammalian cells is catalyzed by several enzymes, including several members of the cytochrome P450 superfamily (CYPs) and FA 2-hydroxylase (FA2H). While some CYPs show high positional selectivity, others are highly relaxed in their regioselectivity and catalyze hydroxylation of FAs merely as a side reaction [226, 227]. A range of different CYP members catalyze the hydroxylation of PUFAs, a necessary step in the synthesis of signaling lipids such as HETEs and EETs (see Section 4.9). FA2H stereospecifically produces a hydroxyl (R)-enantiomer at the second carbon (ω−2) of long chain FAs [228]. *Fa2h* knockout in mice resulted in long-term demyelination and the myelin was found to be lacking in 2’-hydroxy galactosylceramides [229]. One recent study found that FA2H was one of the top 4 downregulated genes in a BC stem cell population when compared to non-stem cell populations, and reported under-expression of FA2H in TNBC [230]. Overexpression of FA2H in a BC cell line reduced the cancer cells stemness, reduced the growth and promoted apoptosis, suggesting a tumor suppressive role for FA2H in BC [230].

4.6 Phospholipid synthesis and membrane remodeling

Cancer cells also frequently show alterations in the expression of enzymes involved in the synthesis and remodeling of PLs. In line with these findings, a substantial fraction of the lipids acquired by cancer cells end up in PLs, which together with cholesterol and sphingolipids are the major constituents of membranes (see Section 6.1). This has been well documented in cancer cell lines with labeled substrates [231]. PLs can be synthesized *de novo* but are also dynamically remodeled. PLs synthesis involves many enzymes, some of these are redundant, that may have different substrate specificities and cell type distributions,

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leading to the well-known diversity of lipid composition in different tissues and/or cell types (reviewed in [232]). Lipid synthesis is also compartmentalized within cells, with different steps taking place in different organelles, mainly in the ER, Golgi and nuclear membrane compartment, resulting in subcellular differences in lipid compositions. For *de novo* PL synthesis, FAs are first incorporated in phosphatidic acid (PA) as the main precursor of PLs. The Kennedy pathway is the main route to synthesize Phosphatidylcholine (PC), the most abundant PL headgroup class in most mammalian cells. The second most abundant PLs are phosphatidylethanolamines (PE), which can be synthesized *de novo*, but can also be generated from phosphatidylserines (PS) by headgroup exchange. PS is synthesized in the ER by headgroup exchange from PC and PE. Phosphatidylinositol (PI) is synthesized *de novo* indirectly from PA. Cardiolipins (CL) are found mainly in the mitochondria where they are synthesized locally. These are important for energy production and the regulation of cell death mechanisms. Sphingosine and ceramides are formed in the ER and transferred to the Golgi where they are used to synthesize sphingolipids or glucosyl- and galactosylceramides. Another important class of lipids are the ether lipids such as plasmalogens, which are ether or vinyl-linked at the 1-position of the glycerophospholipid and of which plasmenylethanolamines are the most abundant. These lipids are synthesized in peroxisomes. Besides *de novo* synthesis and headgroup exchanges, acyl chains of phospholipids are also exchanged in a highly dynamic way. This FA remodeling involves a cycle of diacylation catalyzed by phospholipases which can release acyl chains at different positions depending on the subclass of enzymes (PLA, PLC, PLD), and reacylation or transacylation catalyzed by a class of acyltransferases such as lysophosphatidylcholine acyl transferases (LPCAT).

Intriguingly, many of the enzymes involved in PL synthesis and remodeling are overexpressed in cancer. Lipin-1, for instance, a phosphatidic acid phosphatase (PAP) controlling the rate-limiting step in PL synthesis and co-regulator of transcription factors such as PPARs and SREBPs (see Section 5), is up-regulated in a subset of diverse cancer types including high grade prostate cancer, colon cancer, lung cancer and TNBC [233–235]. High level Lipin-1 expression is associated with poor prognosis and inflammation and downregulation of the enzyme induces ER stress and apoptosis, and attenuates tumor growth *in vivo* in orthotopic xenograft mouse models [233–235].

Choline kinase alpha (ChoKα), the first committed enzyme in in the Kennedy pathway for PC and PE synthesis, is overexpressed in a variety of tumor types and activated by a wide range of oncogenic events. Activation and overexpression of ChoKα has been linked to the increased cellular need for PC, and is a potential biomarker. Knockdown or chemical inhibition of ChoKα causes cell death and attenuates tumor growth *in vivo* [236, 237].

Another class of PL metabolizing enzymes that is implicated in several aspects of tumor biology are the phospholipases. Members of all three subfamilies have been shown to be altered in many cancers. Some isoforms are overexpressed, others are decreased or mutated. Part of their role is related to lipid remodeling but also to the generation of lipids involved in signaling such as arachidonic acid (see Section 6) (reviewed in [238]). The other end product, lysophospholipids (LysoPLs), are elevated in many tumors and have been linked with tumor promotion [20]. LysoPLs are also the substrate for monoacylglycerol lipase

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(MAGL), which is additionally overexpressed in several tumor types and regenerates FAs (see also Section 3). A higher amount of secreted phospholipase A2 is associated with ovarian cancer [239], and phospholipase D mediated release of phosphatidic acid is shown to mediate cell invasiveness in BC models [240]. Intriguingly, a recent report revealed that PLA2G2A is associated with prostate cancer progression and confers ferroptosis resistance to prostate cancer cells by depleting membrane PUFA [241].

Another emerging class of enzymes that appear to be affected in many tumors are the lysophosphatylcholine acyl transferases (LPCATs) that play a central role in the reacylation of lysophospholipids. There are 4 members of this enzyme family, all of which have been implicated in cancer. LPCAT1 has been shown to be overexpressed and to function as a potential prognostic biomarker for many cancer types. LPCAT2 is found in aggressive prostate cancer, LPCAT4 is linked to intestinal stem cell proliferation and tumorigenesis and LPCAT4 is associated with high levels of PC(16:0/16:1) in colorectal cancer [237]. In hepatocellular carcinoma (HCC) cell line experiments, LPCAT1 overexpression enriched PCs and promoted cell proliferation, migration, and invasion, while LPCAT1 knockdown did the opposite (see also Section 5). Thus, LPCAT1 may be a potential target molecule to inhibit HCC progression because it modulates PL composition to create favorable conditions in HCC cells [242].

An intriguing finding is the loss of membrane lipid asymmetry in many cancers. In healthy cells, different headgroup classes of PLs show a differential distribution over the inner and outer membrane leaflet. PS for instance is mainly found in the inner membrane leaflet, where it plays a crucial role in signaling. Under certain conditions, such as induction of apoptosis, this membrane asymmetry is disturbed and PS is exposed on the cell surface where it attracts macrophages for clearance of dead cells. Intriguingly, in viable cancer cells a substantial fraction of PS is found in the outer plasma membrane leaflet and is thought to play a role in immune modulation. These changes are linked with the loss of expression of specific phospholipid scramblases (PLSCRs), enzymes that bidirectionally flip lipids across membranes. Elevated PLSCR1 expression has been found in liver and colorectal cancer for instance [243].

4.7 Lipid oxidation

Cancer cells frequently show changes in enzymes involved in fatty acid oxidation (FAO). The rate-limiting step in this process is the translocation of FA-CoAs across the outer mitochondrial membrane through conversion to FA-carnitine by carnitine palmitoyl transferase 1 (CPT-1). There are 3 paralogs of CPT-1 in mammals; CPT-1A (expressed mainly in liver, prostate), CPT-1B (skeletal muscle, breast) and CPT-1C (brain). In the FAO process, FAs are degraded to acetyl-CoAs that are used in the Krebs cycle for anabolic processes and the production of reducing equivalents to support redox homeostasis. FAO is transcriptionally regulated by the PPAR family of transcription factors (see Section 5), which activate expression of CPT1 and other FAO enzymes in response to glucose deficiency, and post-translationally via allosteric inhibition of CPT1 by malonyl-CoA. The latter is mediated by activation of the nutrient sensor AMPK, which in turn phosphorylates and inhibits ACACA, the enzyme that catalyzes production of malonyl-CoA. It is

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increasingly evident that, despite the widespread focus on so-called Warburg cancers, FAO is an important bioenergetic pathway in many cancers and promotes proliferation, metastasis, stemness and treatment resistance [244, 245] (see also Section 6). In hypoxic conditions or in response to treatment, tumor cells appear to favor FAO to rapidly generate ATP and NADPH and promote survival. Consistent with this concept, clinical BC tissues exhibit enhanced expression of the FAO enzyme CPT1B upon disease recurrence and in response to chemotherapy [149], while CPT1A is higher in chemoresistant pancreatic tumors [246] and associated with poorer outcomes in gastric cancer [247] and acute myeloid leukemia [248]. Moreover, FAO has been identified as a key upregulated pathway and therapeutic target in MYC-overexpressing TNBC [249], thereby linking FA metabolism to oncogenic signaling. It is important to note that oxidation of lipids also takes place in peroxisomes, involving both β-oxidation of very long chain FAs and α-oxidation of branched chain FAs. These processes, and their requisite enzymes, have not been thoroughly investigated in cancer cells and may offer novel opportunities for therapeutic intervention beyond CPT1 in certain cancers that rely on peroxisomal FAO pathways.

4.8 Lipid storage

Depending on the context, a substantial fraction of lipids can be found in lipid droplets (LDs), which are abundant in several cancer types. These organelles are made of deposits of TAGs and cholesterol esters, and are surrounded by a monolayer of PLs. In times of excess lipids, LDs are believed to originate from microdomains in the ER membrane that recruit TAGs. As the TAGs reach the maximum concentration the ER membrane can hold, they start to accumulate between the two membrane leaflets and ultimately separate from the ER through a budding process [250]. LDs are found in many tumor types and in part account for the ‘mobile lipid’ signals in NMR. Clear cell renal cell carcinoma (ccRCC) is one type of cancer that is characterized by a significant accumulation of TAGs in LDs which in addition to glycogen deposits results in its typical histological phenotype. This accumulation has remained poorly understood but one recent study described a role in resisting hypoxic stress. The authors discovered that under hypoxia ccRCC cells release oleate from their TAG stores in an effort to counter the toxic accumulation of saturated lipids which cannot be desaturated by SCD without sufficient oxygen [212]. Accumulation of lipid droplets is a characteristic phenotype of chemoresistant cancer cell lines [251–255], and co-treatment with triacsin C, a non-specific inhibitor of LD biogenesis, has been shown to chemo-sensitize cancer cells [255]. While LD accumulation may in part reflect treatment-induced autophagy, LDs may also serve as an extra source of lipids for FAO under nutrient stress conditions, or as a “sink” to sequester hydrophobic drugs. The terminal step in TAG biosynthesis is catalyzed by the DGAT enzymes, which transfer an acyl chain from fatty acyl CoA to DAG. DGAT1 and DGAT2 both catalyze this reaction but are unrelated genes that evolutionary converged. DGAT1 is overexpressed in prostate cancer compared to normal epithelium and a recent study demonstrated that inhibition of DGAT1 reduced tumor growth in an *in vivo* xenograft model [256]. Conversely, another study showed that DGAT1 overexpression in lung SV40-transformed fibroblasts reduced proliferation and anchorage-independent growth by reducing DAG and PL levels, suggesting that depending on the metabolic context DGAT could function as a negative regulator of tumor progression [257].

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4.9 Signaling lipids

A diverse range of lipids and classes of lipids function as intra- and extracellular messengers to direct cell behavior under normal physiological conditions. When dysregulated in cancer, these signaling lipids can become potent mediators of malignant behavior. Sphingolipids are a class of lipids that contain a sphingoid backbone and important sphingolipid signal mediators are sphingosine, spingosine-1-phosphate (S1P), ceramide and ceramide-1-phosphate (C1P). S1P is produced from sphingosine by sphingosine kinases (SK1 and SK2) and several transcriptomic studies have linked high SK1 and SK2 expression to poor prognosis in BC [258, 259]. S1P can be secreted from cells as well as bind to intracellular targets such as HDAC1/2 and its functional roles in cancer have been described. These include promoting vascularization of tumors [260], progression promoting inflammation through STAT3 [261] and promoting the Warburg effect [262]. Ceramide is converted by ceramide kinase (CERK) into C1P. A BC study has shown that CERK is required for the development and survival of recurrent disease following Adriamycin treatment and that elevated CERK expression is linked with recurrent disease in patients [263]. Classically, ceramide is believed to induce senescence and growth inhibition in cancer, and while a recent study linked high ceramide levels to reduced aggressiveness of BC, other recent studies have suggested the effects of ceramide may be context dependent and rely on the presence of downstream effectors [264]. Both ceramide and C1P are activators of phospholipase A2 (PLA2), an enzyme that functions to release arachidonic acid (AA) for subsequent conversion to prostaglandins (*vide infra*).

Phosphoinositides are a class of lipid molecules that comprise phosphatidylinositol mono-, bis- and trisphosphate and are central mediators of the PI3K/Akt/mTORC1 signaling axis. Activation of PI3K results in the rapid conversion of $PI(4,5)P_2$ into $PI(3,4,5)P_3$ which leads to the activation of Akt. Conversely, the tumor suppressor PTEN dephosphorylates $PI(3,4,5)P_3$ back to $PI(4,5)P_2$ [265]. Recently there has been growing appreciation that $PI(4,5)P_2$ does not only function as a substrate for the synthesis of the growth promoting $PI(3,4,5)P_3$, but that $PI(4,5)P_2$ itself has an important role as a lipid messenger in cancer [265]. Due to specific protein interactions, $PI(4,5)P_2$ has a major role in recruiting cytosolic proteins, facilitating processes like fusion and budding of membranes and the formation of signaling platforms. Local reductions in $PI(4,5)P_2$ are believed to be linked to the regulation of directional movement of cancer cells [266].

Eicosanoids are lipid signaling molecules that are derived from 20 carbon PUFAs, mainly AA and eicosapentaenoic acid (EPA). They function as both autocrine and paracrine signaling molecules to promote or inhibit inflammation or other immune responses. There exist many subfamilies of which prostaglandins, leukotrienes, lipoxins and resolvins are the most well studied. Prostaglandin E_2 (PGE_2) is the most abundant prostaglandin and is a strong mediator of inflammation through binding with the G-protein-coupled receptors EP1 to 4 [267]. Increased levels of PGE_2 have been described in several cancers and are associated with a poor prognosis [268]. The prostaglandin PGD_2 has been less extensively investigated in cancer, but most studies are reporting antitumor activity. A recent study in gastric cancer reported that PGD_2 inhibited tumor growth and suppressed the ability to form metastases [269], while another study in prostate cancer concluded that PGD_2 secreted by

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the stroma can suppress the growth of the tumor cells [270]. Leukotrienes are a type of eicosanoids produced mainly by leukocytes that function in a paracrine manner. Leukotriene LTB_4 is one of the most well studied in cancers and is believed to induce a chronic tumor promoting inflammatory state. In medulloblastoma, blockage of leukotriene synthesis in 5-lipoxygenase–deficient mice dramatically reduced tumor growth *in vivo* [271]. Lipoxins are a type of pro-resolving, anti-inflammatory prostaglandins. Colorectal cancer was found to be associated with overall low levels of lipoxin A_4 and in an *in vivo* xenograft model lipoxin A_4 was able to reduce proliferation of cancer cells [272]. Furthermore in a hepatocarcinoma model lipoxin A_4 reduced the production of vascular endothelial growth factor and reduced tumor growth *in vivo* by impairing tumor-related angiogenesis [273]. Resolvins are another type of eicosanoids with pro-resolving (restoration of tissue homeostasis) and anti-inflammatory action. The release of cytokines from tumor cell debris following therapy is known to stimulate tumor growth. A recent study however found that resolvins can counter the effect of cytokines by attracting debris clearing macrophages [274].

Glycerolipid derived mediators include DAG, LysoPA and LysoPC. DAG is formed during the phospholipase C catalyzed hydrolysis of $PI(4,5)P_2$ and functions as a second messenger that triggers the activation of protein kinase C. In cancer cells, one study showed that resistance to FASN inhibition may be driven by maintaining PKC signaling through sustained DAG levels, and could be overcome by a combinatorial treatment with FASN and PKC inhibitors [275]. LysoPA is generated by the removal of the choline group from LysoPC by autotaxin (ATX), a secreted enzyme. LysoPA exhibits growth factor-like effects through a family of G-protein coupled LysoPA receptors (LPAR) that are highly expressed in several cancers, including lung [276], pancreatic [277] and ovarian cancer [278]. A recent study proposed ATX/LPA signaling as an interesting therapeutic target in liver cancer, as it is involved in both chronic liver inflammation diseases that can progress to cancer and the development of liver cancer itself [279].

4.10 Lipids as membrane anchors and modulators of protein functioning

Lipids also function as anchors to target proteins to membranes in specific locations in cells. Classical examples include palmitoylation, prenylation and farnesylation of proteins, and several key signaling oncoproteins such as Ras, Rho, Wnt and Hedgehog depend on these posttranslational modifications for their functioning [280–282]. In several reports, changes in lipid metabolism in cancer cells are linked to alterations in lipidation and anchoring of proteins. Interestingly, changes in the expression or activity of enzymes involved in protein lipidation have been found in many cancer types. This is evident in the case of farnesyltransferases, which are often overexpressed in tumor cells and are being explored as targets for therapy [283](see Section 8). Recently, also palmitoylation of proteins has become an intense area of research in cancer biology. Several hundreds of proteins that are linked to the oncogenic process are palmitoylated on a cysteine. Some proteins are autopalmitoylated and it has been suggested that overexpression of FASN may be a driver in this process [284–288]. Most palmitoylation processes are however catalyzed by zinc finger DHHC-type palmitoyl S-acyltransferases (PATs), comprising a family of 23 proteins. Acylprotein thioesterases (APT) remove palmitoyl groups from proteins. As nicely summarized by Ko and Dixon [282], some of these proteins are overexpressed in certain

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cancers and may function as oncogenes, whereas others are downregulated and are considered tumor suppressors. Other functions of lipids in the modulation of protein functioning include the modification of Hedgehog by cholesterol [289] and the role of PE as an anchor for LC3 to autophagosomal membranes.

5 Key drivers of alterations in lipid metabolism

In view of the complexity of lipid metabolism and its central role in many biological processes, it is not surprising that this pathway is under tight regulatory control. Aside from a small number of central transcription factors that coordinately regulate enzymes involved in lipid metabolism, this regulation is fine-tuned at several other levels and involves posttranslational and other mechanisms. In cancer, a dramatic rewiring of lipid metabolism takes place that is in part driven by oncogenes and tumor suppressors. Lipid metabolism is also highly adaptive and helps cancer cells to cope in a challenging and changing microenvironment (Figure 2).

5.1 Critical transcription factors in lipid metabolism: SREBPs, LXR, PPARs

Cellular FA and cholesterol acquisition and metabolism are transcriptionally controlled and tightly regulated by two main members of the superfamily of nuclear receptors [290], Liver X Receptors (LXRs) and PPARs and by the basic-helix-loop-helix-leucine zipper (bHLH-LZ) transcription factors (TF) SREBPs [291].

LXRs are TFs of the nuclear receptor superfamily which upon activation form heterodimers with retinoid X receptor (RXR) and bind to LXR response element (LXRE) on the promoter region of target genes. The two isoforms, LXRα and LXRβ, are key transcriptional regulators of lipid and carbohydrate metabolism. LXRs act as sterol sensors protecting the cells from cholesterol overload. They ensure an adequate intracellular sterol content via activation or repression of their direct target genes (respectively ABCA1 and LDLR) [292]. The lipogenic action of LXRs is mediated by direct upregulation of SREBP-1c, FASN and SCD1 [293–296]. LXRs are activated by the oxysterols 22-hydroxycholesterol, 24-hydroxycholesterol, 25-hydroxycholesterol, 25,26-hydroxycholesterol, and 24,25-epoxycholesterol [292]. Apart from LXRs, other nuclear receptors have also been found to be regulated by specific oxysterols. For example, 27-hydroxycholesterol was shown to act as an endogenous selective estrogen receptor modulator (SERM) [297, 298]. LXR has been suggested to be involved in BC and prostate cancer progression [299, 300].

PPARs are part of the nuclear receptor family and play a major regulatory role in energy homeostasis and metabolism. Three nuclear receptor isoforms, PPARγ, PPARα, and PPARβ/δ are encoded by different genes and have different functions. Activation of PPAR-α reduces TAG levels and is involved in regulation of energy homeostasis. PPAR-γ causes insulin sensitization and enhances glucose utilization, whereas activation of PPAR-β/δ increases FA synthesis.

SREBPs are the master regulators of lipid biosynthesis [291]. These TFs regulate lipid homeostasis by controlling the expression of enzymes involved in endogenous cholesterol, FA, TAG and PL biosynthesis [291]. From yeasts to humans SREBPs are highly conserved,

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therefore the expression of lipogenic genes is regulated according to species-specific requirements [301]. As such, SREBP is regulated by palmitate in Drosophila [302], by hypoxia in fission yeast [303] and by sterols in mammals [304]. Different isoforms play different roles in the physiological modulation of lipid synthesis [291]. SREBP1a strongly activates global lipid synthesis and growth, whereas SREBP1c primarily controls energy storage through nutritional regulation of FA and TAG. SREBP2 mediates cholesterol metabolism-related gene expression [305, 306]. However, when overexpressed, the isoforms exhibit functional overlap.

Key events in the activation and regulation of SREBPs involve several steps of trafficking between cellular compartments such as cleavage, recycling and degradation. SREBPs are synthesized as inactive precursor proteins that normally reside in the ER in complex with SCAP (SREBP cleavage-activating protein) and INSIG (insulin-induced gene) [307–312]. In response to sterol depletion, SREBP-SCAP migrate to the Golgi and, through the sequential action of the Golgi-localized Site-1 and Site-2 Proteases, the N-terminal domain is proteolytically released [313]. The cleaved SREBP then translocates into the nucleus where it binds to the promoter of several genes involved in the synthesis, uptake and metabolism of cholesterol and FAs, thus restoring sterol homeostasis in a feedback regulation loop and regulating cellular lipid homeostasis [314]. SREBPs are also affected by FAs and are self-regulated by a transcriptional positive feedback [315–317]. In normal physiology, the SREBP pathways are mostly active in organs involved in the handling and control of lipids, such as the liver and are under tight control by hormones such as insulin. To date, a variety of TFs activated in response to extracellular stimuli has been reported to modulate SREBP transcriptional activity. For instance, LXR activated by oxysterols regulates SREBP activity by direct binding [294, 318, 319]. SREBPs further interact with various transcriptional co-activators such as CBP and p300, which acetylate and stabilize SREBPs by preventing ubiquitination [320, 321]. These modifications regulate the stability and/or transcriptional activity of the active TFs. Transcriptional coactivators and cooperating TFs provide yet another level of regulatory control of SREBP activity [301]. In human hepatocellular carcinoma cells, SREBP1 cooperates with its associated factors, nuclear factor Y (NFY) and simian-virus-40-protein-1 (SP1), to regulate the expression of a subset of target genes through direct interaction [315, 322].

More than 20 years ago SREBPs were shown to be activated in cancer and to contribute to lipid synthesis and uptake [323]. SREBPs are frequently activated through other mechanisms such as constitutive growth factor signaling that functions through the same signal transduction mechanism as insulin [324].

5.2 Growth factor signaling as key driver of lipid metabolism reprogramming

Uncontrolled proliferation is central to tumor development and is regulated by persistent growth factor (GF) signaling. After binding to their receptors generally residing on plasma membranes, GFs activate a signaling cascade triggering a variety of changes in cellular processes allowing growth, division and increase of biomass. Mutations or amplifications of GF genes lead to the constitutive activation of their pathways, further affected by the lipid composition of the membranes in which growth factor receptors (GFR) reside [325].

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EGFR is one of the most commonly activated growth factor receptors in cancers. In prostate cancer cells, the epithelial growth factor activates *de novo* FA synthesis and increases the cellular pool of saturated FAs [80]. Importantly, the upregulation of FASN expression is mediated by EGF-induced activation of SREBP pathway [324]. In non-small cell lung cancer cells, mutated EGFR mediates tyrosine kinase inhibitor resistance through regulation of FASN [287]. Indeed, FASN-dependent palmitoylation of EGFR is needed for EGFR function and kinase activation [326]. EGFR signaling contributes to increased FASN expression in pancreatic ductal adenocarcinoma as well [327]. It has also been shown recently that genetic constitutive activation of EGFR activates LPCAT1, which regulates PL saturation and oncogenic growth factor signaling [14]. LPCAT1 is a key enzyme involved in membrane lipid remodeling that is frequently amplified in cancer and associated with poor patient survival. Using orthotopic glioma cell line xenograft models, as well as lung and renal cancer models, the authors show that knockdown of LPCAT1 suppresses tumor growth and prolongs the survival of tumor-bearing mice [14].

ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2) is a member of the EGFR family of receptor tyrosine kinases. Commonly referred to as HER2, it enhances kinase-mediated activation of downstream signaling pathways, such as MAPK and PI3K–AKT. HER2 is amplified and/or overexpressed in 20–30% of invasive breast carcinomas characterizing a more aggressive disease. Sustained upregulation of *de novo* lipogenesis has been found to contribute to HER2-positive tumor aggressiveness [328]. Overexpression of HER2 in non-transformed epithelial cells induces a lipogenic phenotype similar to that of cancer cells and is dependent on FASN activation [328, 329]. Connections between FASN and HER2 overexpression have been described at a transcriptional level [330] with cellular localization of HER2 changing in response to FASN level and activity. Silencing FASN impinges on the appropriate localization and the membrane accumulation of HER2 altering also the cell morphology [330]. As a consequence, the correct dimerization of HER2 with EGFR is also impaired, blocking a mechanism driving targeted therapy resistance [329, 331]. Overexpression of HER2 has also been found in castration-resistant prostate cancer human samples where FASN is overexpressed. The study showed that progression of prostate cancer toward androgen independence is accompanied by an increase in Her2 expression [332].

Insulin-like growth factor 1 (IGF1) binds to its receptor IFGF-1R initiating a cascade of downstream signaling events leading to activation of the PI3K-AKT/PKB and the Ras-MAPK pathways with consequent increased proliferation and enhanced survival of both normal and cancer cells [333]. The mitogenic activity of the IGF-1R is also mediated by downregulation of cell cycle suppressors and PTEN [334, 335]. Reciprocal rescuing/ activation occurs between IGF-1R, EGFR and HER2 thus conferring resistance to single-agent targeted therapy. In BC, the IGF-1R may contribute to tamoxifen resistance via either an IGF-mediated activation of AKT and subsequent estrogen-independent activation of ERα [336] or via a direct interaction between ERα and IGF-1R [337].

The phosphatidylinositol 3-OH-kinase/ protein kinase B (PI3K/AKT)-mTORC1 pathway is a well-known pro-survival axis constitutively activated in cancer with prominent roles in neoplastic transformation, growth, drug resistance and metastasis [338–340]. The activity of Akt via mammalian target of rapamycin complex 1 (mTORC1) is required for the nuclear

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accumulation of mature SREBP1, directly regulating its expression [341, 342]. SREBP1 function is also essential for Akt/mTORC1-dependent regulation of cell size [203, 341, 343]. In melanoma, the PI3K-AKT-mTORC1-SREBP axis can control cell growth independently of BRAF mutation [340, 344] while in prostate cancer the PI3K-PTEN-AKT pathway was linked to FASN overexpression [92]. The proto-oncogene B-RAF encodes a protein of the RAF family of serine/threonine protein kinases that plays a role in cell division and differentiation by regulating the MAP kinase/ERK signaling pathway. A recent study from our group showed that therapy resistance to vemurafenib in BRAF-mutant melanoma activates sustained SREBP1-driven *de novo* lipogenesis and that inhibition of SREBP-1 sensitizes melanoma to targeted therapy [16].

In breast epithelial cells, the oncogenic PI3K or K-Ras signaling converging on the activation of mTORC1 is sufficient to induce SREBP-driven *de novo* lipogenesis [345]. In addition, oncogenic stimulation of mTORC1 is associated with increased SREBP activity promoting aberrant growth and proliferation in primary human BC samples [345]. The mTORC1-S6K1 complex phosphorylates SRPK2 (SRSF Protein Kinase 2) to induce its nuclear translocation [346]. SRPK2, in turn, promotes splicing of lipogenesis-related transcripts. SRPK2 inhibition results in instability of mRNAs arising from lipogenesis-related genes, thus suppressing lipid metabolism and cancer cell growth. Thus, SRPK2 is a potential therapeutic target for mTORC1-driven tumors [346].

Overexpression of FASN and altered metabolism in prostate cancer cells is associated with the inactivation of the tumor suppressor PTEN [91, 347, 348]; accordingly, PTEN expression is inversely correlated with FASN expression in prostate cancer [349], while inhibition of PTEN leads to the overexpression of FASN *in vitro* [92]. PTEN is a lipid phosphatase and the second most commonly mutated tumor suppressor gene in human cancers. Deletions and mutations in PTEN, are among the most frequent alterations found in prostate cancer, particularly in the metastatic setting [339, 350, 351] suggesting a coordinated feedback between lipogenesis and oncogenic signals to promote tumor growth and progression [88, 350, 352–357].

A concomitant loss of Promyelocytic Leukemia (PML) in PTEN-null prostate cancer is found in 20% of metastatic androgen independent or castration-resistant prostate cancer (mCRPC). PML/PTEN-null promotes metastatic progression through reactivation of MAPK (Mitogen-Activated Protein Kinase) signaling and subsequent hyperactivation of an aberrant SREBP pro-metastatic lipogenic program [358]. Inhibition of SREBP using Fatostatin can block lipid synthesis and metastatic potential [358]. PTEN loss due to mutations or deletions results in PIP3 accumulation and activation of the PI3K/AKT pathway [359, 360]. The PI3K/Akt signaling axis increases the expression of enzymes required for FA synthesis including ACLY, the enzyme catalyzing the production of acetyl-CoA from cytoplasmic citrate, FASN and LDLR [361, 362]. This pathway is responsible for the increase in cell survival, metastasis and castration-resistant growth in prostate cancer. Studies on bone metastasis revealed elevated levels of LDLR that are responsible for LDL uptake and for maintenance of intracellular cholesterol homeostasis [81]. Prostate cancer cells esterify cholesterol in lipid droplets to avoid cellular toxicity due to high intracellular cholesterol

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levels and maintain cholesterol levels independently of the free cholesterol concentration. In this way, cancer cells can keep SREBP constantly active [363].

5.3 Other oncogenes and tumor suppressor genes as drivers of alterations in lipid metabolism in cancer

A range of other oncogenes and tumor suppressors is known to affect lipid metabolism in cancer. c-Myc is an important proto-oncogene TF regulating growth of both normal and cancer cells. c-Myc promotes tumor initiation, progression and survival. MYC is amplified in about 30% of prostate tumors, frequently in the late stages, but is also overexpressed in the absence of a genetic lesion [341, 364]. It has been reported that SREBP2 directly induces c-Myc activation to drive stemness and metastasis in prostate cancer [365] and that SREBP1 promotes reprogramming by interacting with c-Myc in a translocation-dependent manner [366]. SREBP1 interacts with c-Myc facilitating its binding to and promoting the expression of downstream pluripotent targets [366]. MYC regulates lipogenesis to promote tumorigenesis through SREBP1 [367]. Inhibition of FA synthesis blocked tumorigenesis and induced tumor regression in both xenograft and primary transgenic mouse models, revealing the vulnerability of MYC-induced tumors to the inhibition of lipogenesis. Extrinsic risk factors are also able to enrich for MYC signaling. Our group showed that the MYC-transcriptional program can be amplified by a high-fat diet through metabolic alterations contributing to cancer progression and lethality [367].

Upon MYC induction across different cancers, *in vivo* lipidomic changes have been described. We showed that MYC-driven prostate cancer cells are associated with deregulated lipid metabolism *in vitro* and *in vivo*, whereas AKT1 has been associated with enhanced aerobic glycolysis [368]. However, the human data in this study showed metabolic heterogeneity in addition to genetic and signaling pathway heterogeneity. Indeed, heterogeneity in human tumors makes this simplistic interpretation obtained from experimental models more challenging.

The Yes-associated protein (YAP) and Transcriptional coactivator with PDZ-binding motif (TAZ) proto-oncogenes are inhibited by the Hippo tumor-suppressor pathway. YAP/TAZ promote tissue proliferation, organ growth, cancer stem cell properties, metastatic potential and resistance to cancer therapy [369]. Emerging evidence indicates that deregulation of YAP and TAZ mediators of the Hippo pathway signaling may be a major mechanism of intrinsic and acquired resistance to various targeted and chemotherapies promoting tissue proliferation and organ growth [369, 370]. In response to various therapies, numerous upstream signals could impinge on components of the Hippo pathway to activate YAP/TAZ. It has been shown that the SREBP/mevalonate pathway promotes YAP/TAZ nuclear localization and transcriptional activity [371]. Mechanistically, geranylgeranyl pyrophosphate produced by the mevalonate cascade activates YAP/TAZ by inhibiting their phosphorylation and promoting their nuclear accumulation. Thus, these findings indicate that mevalonate–YAP/TAZ axis is required for proliferation and self-renewal of BC cells [371].

The tumor suppressor p53 is a TF that controls the expression of proteins involved in cell cycle arrest, DNA repair, apoptosis, and senescence. p53 also regulates cellular metabolism,

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which appears to play a key role in its tumor suppressive activities [372, 373]. p53 regulates lipid metabolism by transcriptional control or protein–protein interaction. Enzymes affecting lipogenesis whose activities are negatively regulated by p53 include glucose-6-phosphate dehydrogenase [374], which catalyzes the first step in the pentose phosphate pathway. Indeed, loss of p53 activates glucose-6-phosphate dehydrogenase and the pentose phosphate pathway, leading to lipid accumulation [374] while disruption of p53 in ob/ob mice restores the expression of lipogenic enzymes regulated by SREBP-1 [375]. p53 alters the membrane PL composition causing a shift towards a higher degree of saturation. This is mediated by decreased SCD expression through repression of SREBP1. As a consequence, p53-induced changes in PI lipid species attenuate AKT activation contributing to the p53-mediated control of cell survival [376]. More than 50% of human tumors are characterized by mutations of the TP53 gene [350, 377, 378]. Generally, wild type p53 inhibits FA synthesis and lipid accumulation. In contrast, mutant p53 enhances FA synthesis by inhibitory interaction with AMPKα [379]. Previous studies have also suggested that missense mutations confer tumor-promoting functions to p53 [379–381]. A possible mechanism has been proposed where the upregulation of the mevalonate pathway in breast tumors might be mediated by mutated p53 and SREBP and SCAP [382, 383]. Although a comprehensive understanding of the metabolic functions of p53 is yet to be achieved, perturbations of p53-mediated metabolic activities are pivotal during cancer progression as extensively reviewed elsewhere [384–388].

The tumor suppressor protein Retinoblastoma protein (Rb) activates SREBP, leading to activation of the DNA damage response and cellular senescence [389]. In 5% of primary and 37% of advanced prostate cancers, Rb is inactivated, enhancing N-Ras through induction of SREBP1 and 2 [341]. Rb suppresses the malignant progression of tumors in part by controlling the cellular lipid composition. Enzymes involved in elongation and desaturation of FAs, including ELOVL and SCD1, are upregulated by Rb possibly through SREBP. Depletion of ELOVL6 or SCD1 significantly suppresses tumor formation and growth in cell lines and xenografts of Rb-deficient tumor cells [390].

The 5’ adenosine monophosphate-activated protein kinase AMPK is a metabolic sensor and its activation leads to inhibition of metabolic pathways including lipogenesis and cholesterol synthesis. Decreased AMPK activation has been implicated in human metabolic disorders associated with increased cancer risk such as obesity and the metabolic syndrome [391]. AMPK is hypothesized to drive cancer progression by promoting metabolic plasticity, resistance to cellular stress and cell survival. Mechanisms by which the AMPK pathway supports cancer progression include promotion of FAO and increase of intracellular NADPH required to support lipogenesis. The intracellular NADPH level is determined by the difference between its production (generated from the PPP and mitochondrial metabolism) and its consumption (mainly during fatty acid synthesis). Under conditions of energy stress, when NADPH generation from the PPP is impaired, AMPK activation plays a critical role in cancer cell survival by maintaining NADPH levels through inhibition of ACACA and ACACB [392]. It has been shown that AMPK-mediated inhibition of ACACA decreases NADPH consumption in FAS whereas AMPK-mediated inhibition of ACACB increases NADPH generation by activating FAO. However, FAO could also increase the ATP level eventually inhibiting AMPK, therefore the hypothesis that NADPH maintenance rather than

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ATP maintenance is the predominant mechanism by which AMPK promotes cell survival during metabolic stress. In addition, a recently suggested spatiotemporal hypothesis could further explain the context-dependent and time-dependent effects of AMPK regulation in cancer (382). Early in tumorigenesis AMPK may act as a tumor suppressor, but in the advanced stages of the disease it may rather function as an oncogene contributing to therapy resistance and cancer recurrence [396].

In vitro and in pre-clinical models, drug-induced supra-physiological activation of AMPK reduces tumor growth through the suppression of key biosynthetic pathways, most notably lipogenesis [102, 393]. The tumor suppressor role of AMPK has been reported to act through several mechanisms: i) activated by either the STK11/LKB1 tumor suppressor pathway or p53, AMPK blocks *de novo* FA synthesis by phosphorylating acetyl-CoA carboxylase and inducing cell-cycle arrest (metabolic role), ii) induction of mitotic spindle assembly/chromosome segregation abnormalities (non-metabolic role), iii) suppression of the oncogenic MEK–ERK signaling and consequent impairment of cell proliferation and cell-cycle progression via phosphorylation of the oncogene BRAF, iv) counteraction of the epithelial-to-mesenchymal transition, v) loss of AMPK activity contributing to tumorigenesis through hyperactivation of YAP, vi) inactivation of AMPK via ubiquitination and degradation leading to inhibition of autophagy and activation of mTORC1 signaling [102, 393, 395, 397–399].

5.4 Genetic and epigenetic alterations leading to rewiring of lipid metabolism

Chromosome alterations have been proposed to drive cancer progression [400–402]. In particular, chromosome 8 is a hotspot for genomic aberrations comprising not only chromosomal rearrangements and deletions, but also amplifications in several cancer types. The short arm of chromosome 8 (8p) is one of the most frequently deleted genomic regions in a variety of human epithelial cancers [401]. While 8p loss is insufficient to transform cells, it results in the upregulation of the mevalonate and FA pathways. Loss of the 8p chromosome leads to the alteration of lipid metabolism and composition, increasing invasiveness and intravasation and protecting cancer cells from hypoxic stress due to increased autophagy [403]. The human LPL gene is located on 8p22 and plays an important role in lipid metabolism. Lowering or deficiency of LPL expression due to chromosome 8p loss, LPL gene polymorphism, and epigenetic changes in its promoter region are associated with hyperlipidemia and increased cancer risk, especially in the prostate [404–406]. In particular, biallelic inactivation of LPL by chromosomal deletion or promoter methylation has been suggested to contribute to prostate tumorigenesis [407]. Interestingly, an opposite role for LPL was described in cervical squamous cell carcinoma cells where an expressed fusion gene has been identified from novel t(8;12)(p21.3;p13.31) reciprocal translocation [408]. The rearrangement involved LPL and peroxisome biogenesis factor-5 (PEX5). The wild-type LPL overexpression was found to be common in both tissue samples and cell lines. Forced overexpression of wild-type LPL and PEX5–LPL fusion transcripts increased invasiveness in cervical squamous cell carcinoma cells [408].

Chromosome 8q is also the most commonly gained aneuploidy in cancer [401]. In both prostate and breast cancer, chromosome 8 amplification has been associated with increased

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proliferation rates, disease progression and reduced patient survival [409]. A study of 229 primary invasive BC cases identified substantial coamplification of the 8p11-p12 genomic region and the MYC oncogene (8q24.21), as well as aberrant methylation and transcriptional patterns for several genes spanning the 8q12.1- q24.22 genomic region of which one of the rate-limiting enzymes in sterol biosynthesis the squalene epoxidase (SQLE) [410]. MYC activity and DNA hypomethylation may therefore have a pivotal role in the aggressive tumor phenotype frequently observed in BC harboring 8p11-p12 amplification [410]. Another study, involving two independent patient cohorts of 160 patients each, showed that gains of chromosomes 7p and 8q are associated with poor prognosis among ERα positive early stage BC [411]. Whereas SQLE expression levels were not correlated with tumor size, grade, ER status and HER2 expression, there was a significant independent influence on prognosis of the stage I and II study population for SQLE [411]. The correlation between SQLE copy number and expression has been assessed in a large-scale study among more than 8000 cases from 22 cancer types. The authors found the highest prevalence and interaction of SQLE copy number amplification with its gene expression variation in breast, ovarian, and colorectal cancers with BC presenting the strongest association [412]. In particular, SQLE overexpression was more prevalent in aggressive BC suggesting SQLE as a *bona fide* metabolic oncogene by amplification and by being an independent prognostic factor of unfavorable outcome [412]. Overexpression of SQLE has also been found in hepatocellular carcinoma tissues. In hepatocellular carcinoma cells SQLE upregulation promoted cell proliferation and migration, while downregulation of SQLE inhibited tumorigenicity *in vitro* and *in vivo* [413].

An amplification and overexpression of the pyruvate dehydrogenase complex (PDC) has been recently reported in prostate cancer. PDC is responsible of converting pyruvate into acetyl-coA for entry into the TCA cycle in mitochondria [414]. The authors showed that the principal effect of targeting the PDC complex is tumor suppression by abrogating lipid biosynthesis [414].

Genetic alterations of members of the cytochrome P450 superfamily have also been described to play an important role in cancer. The aromatase enzyme CYP19A1 catalyzes the conversion of androgen to estrogen representing a rate-limiting step in estrogen biosynthesis. Aromatase Inhibitors (AI) are used in BC treatment as part of the gold standard endocrine therapy. Amplification of the CYP19A1 gene ($CYP19A1^{amp}$) has been demonstrated to occur in 22% of AI-treated BC patients [415] causing increased aromatase activity, estrogen independent ERα binding to target genes and decreased sensitivity to AI therapy. These data indicate that endocrine therapy selects for acquired $CYP19A1^{amp}$ and promotes local autocrine estrogen signaling in AI-resistant metastatic patients [415]. *De novo* cholesterol synthesis is upregulated in LTED cells (long-term estradiol deprived ERα BC cell lines) via epigenetic reprogramming to promote autonomous ERα activation [416]. Indeed, LTED cells have a ten-fold increase in ERα protein expression [416] despite no evidence of ESR1 amplification or activating mutations [417]. This study suggests that hormone deprivation promotes acquired CYP19A1 amplification that, in turn, triggers ERα activity by converting testosterone possibly obtained via epigenetically driven *de novo* cholesterol biosynthesis. Similarly, CYP19A1 has also been reported to be upregulated in malignant versus benign prostate epithelium, and in metastatic prostate cancer compared to

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localized disease [418]. Another possible mechanism through which BC cells acquire resistance to AI is via a specific drug-induced epigenetic reprogramming that it has been revealed to be activated in AI resistant cells but not in cells developing resistance to Tamoxifen [416]. The AI-induced rewiring consisted in an epigenetic activation of the cholesterol biosynthesis pathway. This work supports the hypothesis that intratumoral *de novo* cholesterol biosynthesis is constitutively activated after chronic exposure to AI leading to the local accumulation of metabolic ligands for ERα such as 27-hydroxycholesterol [297–299, 419].

The cytochrome P450 enzymes sterol 27-hydroxylase (CYP27A1) and oxysterol 7α-hydroxylase (CYP7B1) are responsible for synthesis and degradation respectively of 27-hydroxycholesterol from cholesterol. Mounting evidence suggest that 27-hydroxycholesterol plays an important role in cancer progression. Nelson and colleagues revealed that 27-hydroxycholesterol promotes cell growth and metastasis in mouse models of BC. Dyslipidemia increases the risk of BC through 27-hydroxycholesterol stimulated cell proliferation in ESR-dependent and GDNF-RET (Glial cell line-derived neurotrophic factor-RET)-dependent manners, with 27-hydroxycholesterol accumulation in BC tissue [419]. Importantly, it has been demonstrated that 27-hydroxycholesterol is the first known endogenous SERM [297, 298]. The Nelson lab further showed that 27-hydroxycholesterol is a major biochemical mediator of BC metastasis by increasing the number of polymorphonuclear-neutrophils and γδ-T cells in patients with hypercholesterolemia [420]. CYP27A1 is detected in macrophages within human benign and malignant mammary tissue and in high-grade tumors, and both tumor cells and tumor-associated macrophages exhibited high expression of the enzyme [299]. The expression of CYP7B1 is down-regulated in human BC tissues and CYP7B1 is silenced by epigenetic mechanisms in BC cells [419, 421]. The hypermethylation of *CYP7B1* and recruitment of monocytes likely contributes to the accumulation of 27-hydroxycholesterol in BC and the interaction of 27-HC with macrophages further promotes tumor development [419, 421].

Recent studies described the role of lipid biosynthesis-related epigenetic rewiring in cancer actively contributing to aging, therapy resistance, cellular structural changes and tumor invasive capacity. Methylation of ELOVL2 is highly correlated with the aging process. Impaired ELOVL2 function accelerates aging through disruption of lipid synthesis via increased endoplasmic reticulum stress and mitochondrial dysfunction [422]. In addition, epigenetically upregulated ELOVL2 in glioma stem cells contributes to poor prognosis by driving therapeutic resistance and maintenance of cellular heterogeneity. In contrast, ELOVL2 depletion altered cellular membrane PL composition disrupting membrane structural properties and inhibiting cell growth and tumor initiation [423]. In endocrine therapy-resistant BC cells, epigenetic reprogramming at the type II keratin locus leading to Keratin 80 upregulation drives active cytoskeleton re-organisation and F-Actin remodelling. Chromatin Immunoprecipitation coupled with Next Generation Sequencing (ChIP-seq) revealed that reprogramming is dependent on *de novo* SREBP1 binding to a single enhancer that is activated upon chronic AI treatment. With this study, Perone et al identified a novel and direct link between epigenetic and cytoskeletal reprogramming via SREBP1 promoting cancer cell invasive behavior [424].

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5.5 Regulation by microRNAs

In recent years another layer of regulation of lipid metabolism in cancer involving microRNAs (miRs) has emerged. miRs are small endogenous RNA molecules measuring 18–24 nucleotides in length that occur in eukaryotes only. These regulate post-transcriptional and translational protein expression. Among the lipid-related microRNAs (miRs), miR-33a has been described to be located in the intron of *SREBF2* and miR-33b in the human intron of *SREBF* [425–427]. The miR-33 system regulates lipid homeostasis by modulating HDL biogenesis and cholesterol efflux. miR-33 also targets SREBP1c and has been shown to inhibit BC metastasis [428, 429]. Furthermore, both miR33a [430] and miR-33b [431] were up-modulated after therapy with statins, thus down-regulating the oncogene c-Myc and cell proliferation. Statin treatment has been shown to alter more than 400 miRNAs using *in-vitro* assays (as reviewed in [432]). For instance, the well-known tumor suppressor miR-612 is upregulated after statin intervention, promoting cancer cell differentiation and response to chemotherapy [433]. Another statin-regulated miRNA, miR-182, inhibits the antiapoptotic Bcl-2 transcript consequently favoring cell apoptosis [434]. Two miRs, miR-185 and 342, control cholesterol and FA synthesis in prostate cancer cells by inhibiting SREBP1 and 2 expression and downregulating their target genes, including FASN and HMGCR. Both miRs inhibited tumorigenicity, cell growth, migration and invasion in prostate cancer [427]. Their expression was significantly decreased in tumor cells compared to non-cancerous epithelial cells. It has further been shown that restoring miR-185 and 342 led to caspase-dependent apoptotic death in prostate cancer cells [435]. In glioblastoma, SCAP/SREBP1 activates miR-29 by directly binding to its promoter. A negative feedback loop has been shown for miR-29 that is able to suppress SCAP/SREBP1 and inhibit tumor growth [436].

The miR-22 molecule is involved in the posttranscriptional regulation of ACLY thus supporting metastasis in breast, osteosarcoma, prostate, cervical and lung cancers [437]. A miRNA profile of pituitary oncocytoma reported that the tumor suppressors miR-127–3p and miR-744–5p influenced cell proliferation, carbohydrate and lipid metabolism. In particular, a central role has been proposed for miR-744–5p targeting Aconitase 2 in the regulation of TCA cycle in spindle cell oncocytomas [438].

MiR-497–5p is a known tumor suppressor. miR-497–5p overexpression in HCT116 cells modulated colorectal cancer malignancy via downregulation of IGF1/IGF1-R and inhibition of PI3K/Akt signaling pathway [439]. Another study found that overexpression of miR-497–5p modulates metabolism of the FAs via decreasing ACSL5 levels. The Acyl-CoA Synthetase Long Chain Family Member 5 plays a key role in lipid biosynthesis and FA degradation and is highly expressed in colon cancer cells. miR-497–5p prevents cancer colony formation and negatively regulates cell cycle progression whereas its upregulation increases apoptosis and modulates invasiveness and metastasis in colon cancer cells both *in vitro* and *in vivo*. In patients with colorectal cancer, miR-497–5p downregulation correlated with tumor differentiation, TNM staging, lymph node metastasis and poor survival [440]. Other miRNAs regulating FA biosynthesis identified in malignant pleural mesothelioma, miR-15b-5p and miR-185–5p, have been reported to regulate the target genes FASN, OXSM, ACACB [441].

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In esophageal cancer, miR-142–5p suppresses tumorigenesis by targeting SREBP1. Treatment with Fatostatin in both 2D and 3D cell line models and *in vivo*, resulted in the reduced staining of SREBP1, increased miR-142–5p and suppressed tumor growth [442].

In gastric cancer, miR-671–5p directly interacted with another non-coding RNA, the circPIP5K1A. This is one of the circular RNAs (circRNAs) which have been shown to play a significant role in the initiation or development of human cancers. *In vitro* and *in vivo* experiments indicated that CircPIP5K1A plays an oncogenic role in gastric cancer enhancing cell proliferation, invasion and migration. Mechanistically, the interaction between circPIP5K1A and miR-671–5p modulates Keratin 80 expression forming an axis that contributes to cancer progression through PI3K/AKT pathway [443]. Interestingly, a direct link between SREBP1 activation and invasive behavior via upregulation of Keratin 80 has been previously shown in drug-resistant ER+ breast cancer (*vide supra*, [424]).

In a recent study, starting from metabolic and transcriptomic analysis of renal cell cancer patient tissues, the authors identified upregulated miR-146a-5p that altered the expression of key genes involved in the pentose phosphate pathway and the TCA cycle. They then extended the analysis to more than 6000 patients suggesting that miR-34a-5p, miR-106b-5p, miR-146a-5p, and miR-155–5p are pan cancer microRNAs involved in global regulation of cancer metabolism [444].

Finally, many inflammatory obesity-related miRNAs (inflammatory miRNAs involved in adipogenesis) have been demonstrated to play a role in several cancers (as reviewed in [445]).

5.6 Posttranslational regulation at the level of protein activity, stability and degradation

SREBPs and several other proteins involved in lipid metabolism are also potently regulated at the level of their stability and degradation. It has been demonstrated that the mature forms of SREBPs are modified by phosphorylation [446–450], acetylation [320, 451], sumoylation [320, 451], and ubiquitination [321, 452]. Not only mature, but also SREBP precursor forms are subject to proteasome-dependent degradation via ubiquitylation. Heat shock protein (HSP) 90 regulates SREBP by binding to and stabilizing the SCAP-SREBP complex; inhibition of HSP90 leads to proteasome-dependent degradation of SCAP-SREBP protein [453]. Furthermore, after dissociation from the complex SCAP/SREBP, Insig1 is ubiquitinated and degraded in proteasomes. Ubiquitination is not necessary for release of SCAP/SREBP from Insig1, but it establishes a requirement for synthesis of newly-synthetized Insig1 for feedback inhibition. When the new Insig1 and cholesterol converge on SCAP, SCAP/SREBP binds to Insig1, preventing ubiquitination [454]. As a result, treating cells with proteasome inhibitors increases nuclear levels of SREBPs and target gene expression.

Another mechanism of regulation is provided by ingestion of PUFA, which reduces hepatic SREBP1c activity, thereby decreasing lipogenesis and plasma TAG. PUFA-dependent inhibition occurs by accelerated mRNA decay and proteasomal degradation of nuclear SREBP1c [455–457].

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Kinases play also an important role in posttranslational modulation of lipogenic homeostasis. Protein kinase A (PKA) is a family of enzymes whose activity is dependent on cellular levels of cyclic AMP. PKA inhibits lipogenesis by phosphorylating and disrupting the DNA-binding activity of SREBP1 [458, 459] and phosphorylating upstream LXR [460]. Phosphorylation of SREBP1c by AMPK is necessary for inhibition of its proteolytic processing and transcriptional activity [393, 461]. Moreover, AMPK is also able to block FA and cholesterol biosynthesis through direct phosphorylation of the enzymes HMGR and ACACA. ACACA phosphorylation levels have been found to be increased in invading cells and correlated with metastatic potential in breast and lung cancer patients [462]. In head and neck squamous cell carcinoma, phosphorylation and inhibition of ACACA is followed by a compensatory increase in total ACACA, which rewires cancer metabolism from glycolysis-dependent to lipogenesis-dependent allowing cells to survive cetuximab treatment [463].

Several other proteins involved in lipid metabolism are regulated at the posttranslational level by altering their activity and degradation. The key enzyme in sterol biosynthesis, HMGCR, is degraded by the ER-associated degradation (ERAD) pathway [464, 465]. HMGR degradation is a key aspect of feedback inhibition that is critical for sterol homeostasis in humans. In cancer, degradation of FASN is prevented at the pre-proteasomal level by the isopeptidase USP2a (ubiquitin-specific protease-2a). The deubiquitinating enzyme USP2a associates with and prolongs the half-life of FASN thus playing a critical role in prostate cancer cell survival through FASN stabilization. [466, 467]. The post translational regulation of FASN involves also other factors that promote proteasomal degradation, such as acetylation, thus inhibiting *de novo* lipogenesis and tumor cell growth. In human hepatocellular carcinoma samples, acetylation of FASN is downregulated and expression of the deacetylase HDAC3 and FASN protein levels are increased [468].

The metabolic enzyme ACLY, which plays a pivotal role in promoting cancer metabolism [469, 470], is activated by phosphorylation and acetylation and is degraded by ubiquitination. In cancer, fructose-6-phosphate, provided by glycolysis, promotes phosphorylation of ACLY, thereby enhancing its activity and ultimately contributing to the Warburg effect [471]. Increased phosphorylated ACLY was found in non-small cell lung cancer samples; the authors showed that ACLY phosphorylation, activation and subsequent stabilization is directly mediated by PI3K-Akt pathway [472]. ACLY can also be phosphorylated by other kinases, such as nucleoside diphosphate kinase and AMPK [469]. In lung cancer, acetylation at lysine residues blocks ACLY degradation by ubiquitination further stabilizing the enzymatic activity of ACLY promoting tumor growth and enhanced *de novo* lipid synthesis [473]. The ubiquitin ligase complex is responsible for degradation of ACLY and has often been reported to be down-regulated in lung cancer [474]. Moreover, ubiquitin-specific peptidase 13 (USP13) specifically inhibits degradation and thus upregulates ACLY in ovarian cancer [475].

5.7 Regulation by hormones

Hormones play a crucial role in regulating lipid synthesis in certain cancers. In particular, androgens have a striking effect on lipid metabolism in prostate cancer. It is well documented that the expression of more than 20 enzymes involved in lipid synthesis,

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binding, uptake, metabolism, and transport are regulated by androgens, thereby influencing the entire lipid profile of prostate cells [323, 341, 423, 476–482]. Prostate cancer cells exposed to androgens showed an accumulation of LDs, especially in aggressive metastatic deposits [483], and in circulating prostate tumor cells [484]. This lipogenesis is largely dependent upon increased synthesis of FA and cholesterol [479], is reversed by an AR antagonist and is not observed in AR-negative prostate cancer cells (also referred to as “the lipidic phenotype”).

Currently, the best-characterized mechanism by which androgens may stimulate *de novo* lipogenesis and lipid uptake is through indirect activation of SREBPs [323, 478], although there is evidence of AR binding sites in the vicinity of many lipid metabolic genes that suggest more direct transcriptional regulation [485]. In prostate cancer, SREBP1 plays a crucial role in the activation of the lipogenic phenotype through a described but still incompletely characterized interaction with androgens and AR [486]. Activation of AR by androgens increases expression of lipogenic enzymes in a SREBP1c-dependent manner [480]. A positive feedback loop promotes this signaling pathway since binding sites for SREBP1 are also found in the AR gene [478]. Androgens appear to activate the SREBP pathway with minor effects on SREBP precursor levels and a major increase in the expression of SCAP [477, 479, 487], which in turn plays a pivotal role in the lipogenic effects of androgens in tumor cells [488]. In this positive feedback loop, androgens stimulate the expression of SREBP1 through SCAP [480]. In turn, SREBP1 regulates the expression of the androgen receptor [478, 488].

Elevated levels of SREBP1 protein are found in prostate tumors compared with normal prostate tissue [489]. SREBP1 induces prostate cancer cell proliferation, migration and invasion *in vitro* and promotes prostate cancer tumor growth and castration-resistant progression *in vivo* [486]. In addition, many of the cholesterol synthesis enzymes downstream of SREBPs (HMGCS, SQLE, squalene monooxygenase, lanosterol synthase, farnesyl diphosphate synthase) are elevated during progression of the disease [489]. The clinical and animal data collectively indicate that SREBP1 expression and its nuclear translocation play a critical role in the regulation of prostate cancer development and progression to castration-resistance [486].

Progesterone is an alternative steroidal precursor of dihydrotestosterone [490]. It has been reported that CRPC tumors producing relatively high levels of progesterone are capable of *de novo* synthesis of androgenic steroids [491]. [489, 490]. Progesterone, like dihydrotestosterone, is known to induce cholesterol synthesis in prostate cancer cells [323]. Tumor progesterone levels are high after castration and enzymes necessary for progesterone synthesis from cholesterol (CYP11A1 (Cytochrome P450 family) and StAR (Steroidogenic Acute Regulatory Protein)) and steroids (CYP17A1 and SRD5A1 (Steroid 5 Alpha-Reductase 1)) are increased in CRPC tumors [492]. Compared with untreated primary prostate tumors, castration-resistant metastasis showed a significant increase in the expression of key enzymes required for metabolism of progestins to adrenal androgens and their subsequent conversion to testosterone [493].

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Over the past decades, it has become clear that estrogens also affect lipoprotein metabolism. Estrogens usually decrease serum levels of total cholesterol and LDL-C, and increase HDL-C concentration, but induce an unfavorable increase in serum TG levels [494]. Estrogens can mediate their biologic effects in the liver through binding to the steroid nuclear hormone receptors, ERα or ERβ [495]. Interestingly, over 1000 human liver genes display a sex-driven difference in their expression of which the top biological pathways are in lipid metabolism [496]. [497]. E2 suppresses expression of high-fat diet dependent LXR target genes and TG accumulation through ERα-LXR interactions in mouse liver [498]. Upon E2 stimulation, ERα is recruited to the LXR responsive element in the SREBP-1c promoter in complex with LXRα/RXRα leading to TG reduction [498].

5.8 Adaptive processes and regulation by substrate fluxes

As mentioned in Section 3, lipid metabolism is highly adaptive. Conditions such as nutrient starvation and hypoxia dramatically rewire lipid metabolism. This also involves several of the mechanisms mentioned above. SREBP transcriptional activity, for instance, was shown to be induced by serum depletion both in normoxic and hypoxic cells and activation of SREBP was required to maintain the expression of FA and cholesterol metabolism genes under hypoxic conditions [211]. Additionally, hypoxia-induced expression of SCD, FABP3 and FABP7 was strongly dependent on SREBP function. Inhibition of SREBP blocked lipid biosynthesis and impaired cell survival in a three-dimensional spheroid hypoxic cancer cells model.

In liver and lung carcinomas desaturation of palmitate to the unusual FA sapienate, supports membrane biosynthesis during proliferation [216]. Sapienate biosynthesis enables cancer cells to bypass SCD-dependent FA desaturation. The authors reported that targeting both desaturation pathways was required to inhibit proliferation *in vitro* and *in vivo*. Consistent with these and other reports [15, 499, 500], Bi et al recently demonstrated that membrane lipid saturation is essential for oncogene-driven cancer development [14]. Finally, membrane phospholipid remodeling generates an actionable dependency across cancers.

Cancer cells grown in lipid-reduced conditions become more dependent on *de novo* lipid synthesis pathways and are more sensitive to inhibitors of lipogenic pathways [181]. Cancer cell lines like breast and prostate have more lipid rafts and are more sensitive to cell death induced by cholesterol depletion than their normal counterparts. Cholesterol-rich lipid rafts facilitate the accumulation of receptor tyrosine kinases, such as HER2 and IGF-1, to rapidly induce oncogenic signaling [501, 502].

At the intracellular level, cholesterol derivatives such as cholesteryl esters (CE) and oxysterols play important roles in cancer. The acetyl-CoA acetyltransferase 1 (ACAT1) is the key enzyme that converts cholesterol to CE, usually stored in lipid droplets [503]. ACAT1 appears to exert a pro-tumor function in many cancer cells, such as pancreatic [483] and breast cancer [504]. In xenograft models of pancreatic and prostate cancer, blocking ACAT1 markedly represses tumor growth [483, 505]. CE accumulation is a consequence of PTEN loss and subsequent activation of PI3K/AKT pathway in prostate cancer cells [483].

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Other CE-metabolic enzymes are highly expressed and function as key players in controlling cholesterol esterification and storage in tumors, including sterol O-acyltransferase 1 (SOAT1) and lysosomal acid lipase. Targeting SOAT1 suppresses glioblastoma growth and prolongs survival in xenograft models via inhibition of SREBP-1-regulated lipid synthesis [506]. The knockdown of SOAT1 alters the distribution of cellular cholesterol, and effectively suppresses the proliferation and migration of hepatocellular carcinoma cells [507]. Lysosomal acid lipase is upregulated and promotes cell proliferation in clear cell renal cell carcinoma [508]. Interestingly, HIF has been reported to control FA metabolism contributing to renal cell carcinoma tumorigenesis [505]. HIF directly represses the rate-limiting component of mitochondrial FA transport, carnitine palmitoyltransferase 1A, therefore reducing FA transport into mitochondria and increasing lipid deposition in clear cell renal cell carcinoma [509]. Hypoxia-induced-lipid storage has also been demonstrated to serve as a protective barrier against oxidative stress-induced toxicity in breast and glioma cell lines due to a HIF1α-dependent increase of FA uptake via FA binding proteins FABP3 and FABP7 [510].

The PI3K-AKT-SREBP pathway controls *de novo* lipid biosynthesis through glucose and glutamine [203]. Rapidly proliferating tumor cells depend more on glucose and glutamine for extensive *de novo* lipogenesis because of the action of oncogenic growth signaling molecules. Some cancer cells preferentially use glutamine as the main precursor to synthesize FA by reprogramming glutamine metabolism (glutaminolysis). Previous findings showed oncogenic levels of MYC to be linked to increased glutaminolysis resulting in glutamine addiction of MYC-transformed cells [363, 511]. SREBP can directly induce glutamine-derived carbon flux into lipid precursors at the sacrifice of the normal tricarboxylic acid cycle. As a result, cancer cells do not simply shift to an anabolic phenotype, but they rather actively reprogram their metabolism via SREBP [344].

6 Lipids as central players in cancer biology

Lipids are involved in numerous cellular processes, many of which are linked to the oncogenic process. In addition to the classical roles of lipids as building blocks for membranes and energy sources, evidence is emerging that altered lipid metabolism plays a central role in supporting cancer cell growth and survival in a changing and hostile environment (Figure 3).

6.1 Feeding membrane production and cell proliferation

Consistent with the intuitive concept that rapidly proliferating cancer cells require more lipids for membrane synthesis, lipids that are acquired by cancer cells from the microenvironment or by *de novo* synthesis largely end up in cellular membranes [15, 97, 478, 512–514]. That is the case for both phospholipids and cholesterol, which are the major building blocks of membranes. Early experiments with cell cultures indicated that inhibition of FA synthesis by knocking down or chemical inhibition of key lipogenic enzymes such FASN or ACACA dramatically decreases the size and membrane content of cancer cells to almost half of the original levels [15, 97, 514]. Concomitantly, cells stop proliferating and ultimately die [15, 97, 181, 513]. Supplementation with external lipids can, but not always

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[515], reverse these effects [515], indicating that while lipid acquisition either through *de novo* lipogenesis or uptake supports membrane formation and cell proliferation, *de novo* synthesis occurs in cancer cells even with an adequate extracellular lipid supply. Similar findings have been made in numerous other cell lines and models. Several studies have also found a link between lipogenic enzymes such as FASN and the proliferation marker Ki67 [89]. Nevertheless, activation of lipogenesis and other alterations in lipid metabolism are also observed in cancer precursor lesions where cell proliferation is low, pointing to other roles than mere bulk membrane synthesis for proliferation [89].

6.2 Balancing lipid content and protecting cells from lipotoxicity

Besides providing biomass for cell proliferation, lipid metabolism helps the cancer cell to adapt to a changing environment and to keep the lipid composition within a narrow range of variation. In fact, the lipid composition of membranes dramatically affects their biophysical properties and functioning. In this context, a plethora of reports highlight the frequency of membrane lipid desaturation in lipogenic cancers, which balances saturated and unsaturated fatty acid content to avoid lipotoxicity and ER stress [516]. In fact, saturated fatty acids, the direct end products of FASN, are toxic to cells at high levels and induce an ER stress response and cell death unless a substantial fraction is desaturated by desaturases such as SCD1, which accordingly are overexpressed along with FASN in lipogenic tumors [517, 518].

MUFA-PUFA balance is also suggested to be just as carefully controlled, since PUFAs render membranes more sensitive to lipid peroxidation and ferroptosis [519] (see Section 6.5). Recent evidence from cancer cell lines exposed to exogenous FAs confirms that membrane lipid composition can be modulated only to a certain extent and that excess lipids are stored in LDs. For instance, when cancer cells are challenged with exogenous DHA, a 2-fold increase in DHA levels is observed in membranes, whereas their levels in triacylglycerides are increased by more than 100-fold. Similar effects are observed in cells exposed to saturated FAs (JD, unpublished data). Furthermore, it was recently shown in prostate models that increased lipid uptake stimulates FA storage preferentially into DAGs and TAGs, and to a much lesser extent into phospholipids [159]. These findings are consistent with the emerging concept that LDs play a central role as a sink to keep the cellular balance of FAs in a narrow range and to sequester excess PUFA to protect cells from ROS, as detailed in 6.5.

This sequestration of lipid may also play an important role in the regulation of lipid composition under stress conditions such as hypoxia. For example, FA desaturation requires strong reducing equivalents and oxygen, which can be particularly limiting in the hypoxia characteristic of solid tumors. In glioma models, the SREBP dependent lipogenic program and SCD are more highly expressed in hypoxia, and this is in part shown to compensate for the reduced availability of oxygen [211]. Renal carcinoma cells store MUFAs such as oleate into TAGs in conditions of less extreme hypoxia. Under extreme hypoxia where desaturation becomes challenging, MUFA from TAGs can be hydrolyzed and assembled into PLs, providing a buffer to allow the cancer cell to maintain membrane desaturation [212].

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A final example of how alterations in lipid metabolism function in the detoxification of certain lipids is the observed overexpression of the enzyme α-methylacyl-CoA racemase (AMACR) in prostate cancer [520, 521]. AMACR is involved in branched FA oxidation and is shown to be necessary for proliferation of prostate cancer cells *in vitro* [522] through detoxification of dietary methyl-branched lipids [523] and other mechanisms detailed below.

6.3 Empowering cellular processes

Since the 1920s it has been known that cancer cells largely rely on glucose for energy production [2]. However, it is now established that glucose is also preferentially used as a carbon source for anabolic processes [524–527]. Lipids can provide a large quantity of energy in addition to reductive and anabolic equivalents for a proliferating cell. Together with the observations that several cancers are shown to stimulate lipolysis and take up FAs from surrounding adipose tissue [528–532], this suggests that obtaining FAs for oxidation could be important for cancer cells.

There is substantial evidence that lipids are a relevant source for energy production. In physiology, FAO occurs in tissues with a high energy demand like heart and skeletal muscle [244]. Furthermore, in situations of increased ATP demand, such as loss of attachment to the extracellular matrix by cancer cells, FAO is required for ATP production and cell survival [533, 534]. Moreover, it was recently shown that upon acidosis stress, FAO is increased to generate ATP and drive metastasis through stimulation of early steps such as invasion and resistance to anoikis [535]. Interestingly, metastatic cells found in the lymph nodes were recently shown to have altered their metabolism towards FAO in order to adapt to the lymph node environment [369]. Furthermore, another study recently demonstrated the role of FAO-driven ATP production in glioblastoma tumorigenesis [536], and FAO-derived ATP synthesis has been shown to drive chemoresistance in BC and leukemic stem cells [537, 538]. FAO can also drive anabolic reactions through production of FA-derived carbon in the form of acetyl-CoA. Interestingly, it was shown that in endothelial cells, acetyl-CoA produced through FAO is essential for *de novo* nucleotide synthesis [539]. In this way, FAO drives pathological angiogenesis *in vivo*.

6.4 Membrane biophysics and oncogenic signaling and metastasis

Membrane lipid composition is known to dramatically alter membrane function [540] and, in particular, membrane fluidity. PLs containing saturated FAs have straight acyl chains that pack densely and thus decrease membrane fluidity. As double bonds result in a kink in the acyl chain, unsaturated FAs pack less densely and increase membrane fluidity. Also changes in cholesterol, which are often observed in tumors, dramatically affect membrane fluidity [541, 542]. Evidence from several teams, including ours, has shown that *de novo* FA synthesis and the subsequent changes in membrane lipid composition affect both lateral membrane fluidity (within a membrane leaflet) and transversal membrane fluidity (between leaflets). We previously showed that these changes in membrane fluidity also affect the uptake of certain chemotherapeutics such as doxorubicin that traverse the membranes through a flip-flop mechanism [15]. Moreover, increased membrane fluidity is shown to stimulate metastasis in lung cancer [543], and correlates with a poor prognosis [544]. These findings demonstrate that balancing saturated and unsaturated FAs in membrane lipids is not

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only important in preventing lipotoxicity and lipid peroxidation, but also affects biophysical properties of the membrane with far-reaching consequences.

Moreover, according to the current concepts, membrane lipids are not uniformly distributed but, depending on their biophysical properties, tend to cluster into specific microdomains. Although microdomains with several different compositions exist, they are overall enriched in sphingolipids and cholesterol [545]. By their specific lipid composition, these nano-scale subdomains in the plasma membrane create optimal biophysical conditions for certain signaling proteins to be recruited and to cluster [545]. Therefore, they often act as platforms for growth factor or cell death receptor signaling. Cellular signaling by receptor tyrosine kinases (RTKs) at the plasma membrane is facilitated by transient lipid microdomains termed lipid rafts [546, 547]. Furthermore, cholesterol-rich lipid rafts allow the accumulation of RTKs such as HER2 and IGF-1, to rapidly induce oncogenic signaling [501, 502]. Early evidence from one of our teams has shown that *de novo* synthesized FAs largely end up in detergent-resistant microdomains [548]. Together with the observation that acyl chains of phospholipids in lipid rafts are generally more saturated [549], this suggests a role for *de novo* lipogenesis in oncogenic signaling through lipid rafts. Furthermore, a recent study in glioma models shows that increased saturation of plasma membrane phosphatidylcholine species mediated by LPCAT1 enhances EGFR clustering and activation [14] (see also Section 5). Another recent study showed that ELOVL2-dependent accumulation of PUFA at the plasma membrane is required to promote EGFR signaling, also in glioma models [224]. Therefore, the contribution of membrane lipid changes to oncogenic signaling appears to be complex and multifactorial. As described in Section 4.10, lipids can also regulate signaling through post-translational modifications of proteins. It is well established that prenylation or palmitoylation of important oncogenes like EGFR and RAS is essential to their localization and function, and targeting these post-translational modifications holds promise in pre-clinical models, although only limited clinical efficacy was observed thus far [282, 550]. Overall a concept is emerging that alterations in lipid metabolism in cancer play a central role in feedforward oncogenic signaling. Moreover, altered sphingolipid metabolism, as occurs in many cancers, reduces the levels of the pro-apoptotic lipid ceramide and increases the levels of key proliferative signaling lipids such as sphingosine-1-phosphate (S1P), leading to extensive efforts to modify this pathway pharmacologically (reviewed in [551]). Recent observations suggest that lipid metabolism also contributes to cancer development by inducing epigenetic changes. In fact, FAO-derived acetyl-CoA is shown to be a carbon source for histone acetylation in octanoate-treated hepatocytes and BC cells [552]. However, this finding contradicts earlier claims that FAO does not result in nucleocytoplasmic acetyl-CoA and does not contribute to histone acetylation [553]. Therefore, there is a need for more research on the context-dependent role of FAO in epigenetic regulation.

6.5 Protection from oxidative stress

Cancer cells often contain high levels of reactive oxygen species (ROS), arising due to oncogenic transformation, altered metabolism, deregulated redox homeostasis and hypoxia. Increased ROS has been shown to contribute to genomic instability and tumorigenesis. However, a critical balance needs to be maintained as excess ROS can induce cell death

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[554–556]. It is well known that PUFAs are more susceptible to peroxidation than saturated or monounsaturated lipids [519]. In fact, peroxidation of PUFA is a key driver of ferroptosis, a newly-recognized form of cell programmed death [557, 558]. To protect cancer from the deleterious effects of ROS, a plethora of mechanisms employed by cancer cells have recently been described. One of these is the degradation of lipid hydroperoxides by GPX4, a lipid hydroperoxidase that can selectively degrade lipid hydroperoxides from the membrane. In multiple cancer models, GPX4 is a central driver of ferroptosis resistance [559, 560]. Although GPX4 is a key protective enzyme against ferroptosis, several reports have identified other players that are required for ferroptosis that are dominant over GPX4. A CRISPR screen of cells knocked out for GPX4 surprisingly found that cells lacking both GPX4 and ACSL4 were resistant to ferroptosis. Mechanistically, ACSL4 is required to enrich membranes with PUFA and thereby drives a vulnerability to membrane lipid peroxidation [561].

Another mechanism cancer cells use to decrease their levels of PUFA in membranes and to protect themselves from ROS is the activation of fatty acid synthesis. Since human cells lack the enzymes required to generate essential PUFAs, increased lipogenesis not only provides the cancer cell with membrane biomass but also increase its relative degree of saturation. We and others have shown that *de novo* lipogenesis effectively leads to membrane lipid saturation and depletes polyunsaturated FAs from the cell membrane, and thereby protects cancer cells from lipid peroxidation and ferroptosis [15, 16, 562]. Similarly, membrane mono-desaturation mediated by SCD in ovarian cancer models [206] or the uptake of MUFAs and incorporating them into membrane PLs has been shown to provide a robust protection from ferroptosis [218]. Along the same lines, it was recently shown that PUFA incorporation into TAGs can protect them from lipid peroxidation and ferroptosis [241, 563]. Furthermore, the rate-limiting enzyme for FAO of PUFAs, DECR1, promoted prostate cancer cell survival by protecting cells from lipid peroxidation and ferroptosis [564]. As mentioned above, FAO derived NADPH can be used to maintain antioxidant potential via the glutathione recycling system [392, 565]. For these reasons, in periods of nutrient deprivation or ROS stress, cancer cells may rely more heavily on FAO. A study in melanoma shows that under ROS stress and MAPK inhibition, FAO is required for melanoma cell survival [161, 566]. Moreover, FAO inhibition was shown to be toxic in an oxidative subset of diffuse large B-cell lymphoma cells where it interfered with glutathione generation [567]. Furthermore, sustained FAO drives metastatic colonization of BC via protection from oxidative stress [568]. It is therefore tempting to speculate that FAO plays a key role in ferroptosis resistance. Indeed, inhibition of FAO induced ferroptosis sensitivity in ccRCC, although the contribution of NADPH was not assessed [569]. Furthermore, in two back to back papers, screening for genes that can complement the loss of GPX4 further implicates the mevalonate pathway and NADPH generation in identifying FSP1 as a driver of ubiquinone recycling. Ubiquinone was identified as a potent antioxidant that was sufficient to compensate for GPX4 loss [570, 571]. Furthermore, anaplastic large cell lymphoma models and cell lines have been shown to generate high levels of squalene, which is identified as an endogenous antioxidant that protects the cells from ferroptosis. Interfering with squalene synthesis is therefore a promising strategy in this cancer [572].

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The ability of lipid metabolism to regulate reductive equivalents is not restricted to the process of FAO. Interestingly, a recent finding shows that sustained membrane lipid desaturation is critical in physiology not merely due to its products, but due to the fact that the enzymatic reaction consumes NADH and generates NAD+ [225]. Much like lactate production, the increased availability of NAD+ is required to sustain glycolysis, although the contribution of this mechanism in cancer is unknown.

6.6 Signaling in the microenvironment

Lipids function as precursors for important intracellular signals such as diacylglycerol and phosphatidylinositol phosphates (PIPs), which are often deregulated in cancer and involved in cell motility and tumor progression [266] (See also Section 4 of this review). Furthermore, FAs are precursors of extracellular signaling lipids which include the diverse class of oxylipins, LPA, ceramide and sphingosine-1-phosphate. The intracellular pool of free FAs is very limited since the majority of FAs are rapidly incorporated into membranes and neutral fats. Therefore, the liberation of FAs from phospholipids or neutral fat is necessary in the generation of free FAs and lysophospholipids (LysoPLs). Compared to the metabolic contributions of lipids, the oncogenic roles of this source of FAs has only recently come to light [573].

FAs can also be released from neutral fat stores by the enzymes ATGL, HSL and MAGL [574]. ATGL in particular has been shown to have oncogenic roles in colorectal and lung cancer cells [575, 576], and may contribute to BC growth and invasiveness by releasing adipose derived FAs [577]. A pharmacological inhibitor of ATGL is available [578] and ATGL has been shown to have pro-tumorigenic roles in multiple cancer models; mice lacking ATGL spontaneously form tumors [576] and ATGL protects cells from lipid peroxidation and ferroptosis. MAGL, which hydrolyses monoacylglycerol, has been shown to contribute to cancer progression and aggressiveness, in driving an array of oncogenic signaling pathways including synthesis of prostaglandins, LysoPLs and ether lipids [579]. However, it can also play key immunosuppressive functions in tumor-associated macrophages (TAMs) [580]. Inhibition of MAGL by the small molecule JZL184 or knockdown suppresses tumorigenesis of melanoma and ovarian cancer cells [581]. However, not all studies support a pro-tumorigenic role of phospholipases in cancer. Indeed, their expression is often lowered in cancers [582], perhaps in a context-dependent manner. The lysis of adipose-derived FAs may also provide the cancer cells with free FAs and FA-derived signaling molecules that can drive cell invasiveness. In pancreatic cancer cells, the secretion of the extracellular autotaxin provides stromal-derived LPCs which can be used to generate LPA, thereby powering cancer cell invasiveness [583]

PUFAs such as arachidonic acid can be modified and oxygenated in order to generate a highly diverse and complex class of molecules termed oxylipins. These metabolites can have profound effects on multiple aspects of tumor biology, including mediating cell invasiveness and immune evasion as detailed below in Section 6.7.

Cancer cells have long been shown to generate lipid-enclosed microvesicles such as exosomes, microsomes or oncosomes. These microvesicles are taken up by nearby stroma and distant tissues and can exert potent effects at target sites [584]. In particular, an elegant

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study shows that the specific distribution of integrins found in exosomes dictates their binding to target organs and thereby results in inflammation, and prepares the site for the eventual establishment of metastases [585]. Although the biological role of exosomes in cancer biology remains underexplored, the unique RNA, protein and lipid cargo contained in these circulating vesicles can almost certainly have significant biological effects [586] (See also Section 8). The vesicles may also deliver enzymes involved in lipid metabolism [587].

6.7 Immune-modulation

One of the established hallmarks of cancer is the evasion from immune surveillance, a phenomenon that is successfully targeted using immune checkpoint inhibitors, which currently are revolutionizing cancer therapy. However, many patients fail to respond to this therapy through primary or acquired resistance mechanisms [485]. Findings showing the importance of lipid metabolism in functioning of the immune system therefore offer exciting new opportunities to address this issue. A recent report shows that interferon gamma induces cell death in cancer cells by inducing ferroptosis and points towards the importance of lipid metabolism in the context of clinical treatment with immune checkpoint inhibitors [588]. Cancer cells not only suppress immune cell function but can convert the immune system to sustain tumor growth. In ovarian cancer for instance, cancer cells are shown to promote the efflux of cholesterol from macrophages which in turn drives a pro-tumoral M2 phenotype [589]. PGE2 is the most well-described oxylipin in cancer, which has a dominant suppressive role on the immune environment and leads to the failure of immune-cell cancer clearance in addition to its pro-inflammatory and angiogenic roles. Although PGE2 can be produced by cancer cells, recent evidence shows that PGE2 is primarily produced by tumor-associated myeloid-derived suppressor cells in a FATP2 dependent manner [590]. The FATP2 FA transporter plays critical roles in tumor associated neutrophils to transport arachidonic acid for the synthesis of prostaglandin E2, as interference with this process abrogated tumor growth [590]. These and other findings suggest the importance of lipid metabolism in the clinical response to immunotherapy. Although the roles of other oxylipins such as leukotrienes and resolvins is well appreciated in the context of asthma and inflammation, their contribution to cancer remains less well understood. This is in part due to their low abundance and technical challenges in their measurement. With their potent effects on multiple aspects of biology including immune cell chemotaxis and function, this is likely to be an emerging and important field in the context of cancer biology and immunotherapy. Moreover, several recent studies have highlighted the critical role of lipid metabolism in immune cell functions and therefore caution against a systemic approach in targeting lipid metabolism. Both FA synthesis and oxidation are important regulators of immune responses. FA synthesis plays a role in antigen presentation and T cell activation, whereas FAO regulates hematopoietic stem cell maintenance. In a nutrient deficient tumor microenvironment, CD8+ T cells require FAO to efficiently clear melanoma cells [591]. This is compounded by further evidence showing that FAO may increase the prevalence of cancer neoantigen presentation and correlates with a good response to immune checkpoint inhibitors [592]. Also cholesterol metabolism may play key roles in the formation of an effective T-cell receptor complex and therapeutic interference may therefore be detrimental to T-cell function [593]. Moreover, there is evidence that the rapid expansion of T-cells requires SREBP mediated lipogenesis [594]. The externalization of phosphatidylserine, a

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hallmark of the apoptotic process, has also gained increasing interest recently due to its immunosuppressive action that promotes the tumor's immune evasion [595]. Also acid sphingomyelinase (ASM) which is required for the conversion of the cell membrane component sphingomyelin into ceramide has been shown to elicit an effective antitumor immune response by the host [596]. As a significant portion of preclinical cancer models use immunodeficient mice, the potentially profound effects of lipogenic inhibitors on immune cell function is completely missed.

7 Lipids as biomarkers for cancer

A growing body of evidence indicates that the rewiring of lipid metabolism in cancer holds potential for the development and use of biomarkers. A large number of studies have shown that enzymes involved in lipid metabolism are differentially expressed in tumors and, depending on the enzyme and tumor type, correlate with stage or grade, or have diagnostic or prognostic potential. So far, few of these markers are currently being used in the clinic.

Driven by recent technological developments in the analysis of lipids and the recent explosion of lipidomic studies of experimental cancer models and clinical specimens, the potential of the lipidome to yield novel biomarkers in cancer has attracted considerable interest as a complement to other, predominantly genomic markers [33, 597, 598]. Initial studies focused on cancer biomarker discovery were largely qualitative and exploratory in nature with relatively small patient numbers, and sought to identify lipids associated with the presence of cancer, certain clinical features or patient outcomes (for a recent comprehensive overview of lipid biomarker studies undertaken in cancer the reader is referred to Bandu *et al*, 2018 [598]).

7.1 Lipid metabolism enzymes as potential biomarkers

As mentioned in the previous sections, there are numerous reports on the altered expression of enzymes involved in lipid metabolism in almost all tumor types. In some studies, claims have been made on the potential use of these proteins as biomarkers for diagnosis, stage or grade, or disease progression. Such claims have been made for instance for FASN, FABPs and many others. Caution has to be taken that few of these findings have been confirmed in large cohorts of patients and many of the claimed associations cannot be confirmed in TCGA data for several reasons. Several enzymes involved in lipid metabolism are also found in body fluids such as serum or plasma. That is for instance the case for FASN, FABPs and LSCR1, suggesting that these proteins might be used as a noninvasive serological diagnostic and prognostic biomarker for cancer [599]. However, none of these proteins are routinely used in the clinic as biomarkers.

7.2 Lipidomics in biofluids

The potential for lipids as biomarkers has come to the forefront thanks to great advances in technologies enabling the quantitative analysis of complex lipids, including mass spectrometry-based lipidomics as detailed in section 3, and fatty acids measured by GC-MS. So far, the majority of lipid profiling studies in patient samples have been undertaken in biofluids, which offer patient-friendly sources of biomarkers without the invasive nature of

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tissue biopsies or heterogeneity of tissue sampling. An ever-expanding number of studies have used MS-based lipidomics or metabolomics to identify individual or groups of lipid species in serum or plasma that can distinguish between cancer patients and cancer-free controls (reviewed in [597, 598]). While patient numbers are often low and factors such as patient fasting status or metabolic medications can be confounders, several recent larger-scale lipidomics studies have provided compelling evidence for the potential of the lipidome to provide diagnostic and clinically-actionable prognostic biomarkers in a range of cancers (Table 1 and Table 2). Identified signatures comprising relatively small numbers of circulating lipids or fatty acids had the capacity to distinguish breast [600, 601], ovarian [22], colorectal [602] liver [23], lung [24, 25] and prostate [26, 603] cancer patients from cancer-free controls. Of arguably greater clinical significance, lipid profiles have also been shown to have prognostic value for cancer development [604][603, 605, 606], aggressiveness [607], therapeutic response [608–610] and patient survival [611].

While plasma lipidomics has not yet experienced widespread clinical implementation, the increasing use of accredited MS-based blood lipid profiling platforms for clinical diagnosis of inborn errors of metabolism and other metabolic disorders provides feasible opportunities for rapid clinical implementation of circulating lipid biomarkers in cancer. The current priority to develop guidelines for plasma lipid profiling will further assist in implementation and validation of such testing [612], as it is currently difficult to compare lipidomic data between studies due to variation in MS platforms, data normalization and processing. The next key conceptual step for plasma lipidomics is linking lipid-based risk profiles to an underlying biology in order to most appropriately design therapeutic or preventive strategies. Beyond plasma, there has been interest in lipidomic profiling of urine [613, 614] and extracellular vesicles [615] that may also prove informative as non-invasive sources of cancer biomarkers.

7.3 Tumor lipidomics

For clinical tissue specimens, instrument sensitivity initially constrained lipidomic analysis of the often limited quantities of cancer tissues available. This meant that early studies were mostly undertaken using cell line models. The numbers of different lines analyzed in these studies are often small, thus limiting their value for clinical biomarker discovery. Nonetheless, these studies have provided the first detailed information about the lipidomic features of cancer cells that impact on various aspects of cancer cell behavior, how these profiles change in response to treatment, and clues as to the initiating factors that drive certain cancer-related lipid profiles. For example, in 2010, Rysman *et al.* investigated phospholipid composition in prostate cancer cells using electrospray ionization (ESI) tandem mass spectrometry (ESI-MS/MS) and concluded that these cells commonly feature a lipogenic phenotype with a preponderance of saturated and mono-unsaturated acyl chains due to the promotion of *de novo* lipogenesis [15]. These features were associated with reduced plasma membrane permeability and resistance to chemotherapeutic agents. Sorvina *et al* showed using LC-ESI-MS/MS that lipid profiles could distinguish between different prostate cancer cell lines and a non-malignant line and, consistent with their MS data, staining for polar lipids showed enhanced signal in cancer versus non-malignant cells [616]. A study from 2015 by Burch *et al.* integrated lipidomic with metabolomics profiling (LC-

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ESI-MS/MS) using bioinformatics to identify and quantify differentially regulated molecules in five prostate cell lines. Their data revealed upregulation of multiple phospholipid classes and other metabolites in all malignant lines, but suggested that different lipogenic pathways are activated in metastatic cells as compared to non-metastatic and normal prostate cells [617]. Analysis of lipid and fatty acid content of breast [618] and melanoma [619] cell lines with differing metastatic potential revealed that higher levels of phospholipids containing SFA and MUFA chains (C16:0, C18:0, C18:1) were associated with greater metastatic potential. Importantly, the discovery by Roy et al (2019) of diacylglycerols being overexpressed in metastatic vs non-metastatic osteosarcoma lines allowed pharmacological targeting of diacylglycerol synthesis, which reduced cell viability and migration and provided proof of principle that certain lipidomic changes in cancer cells can support the cancer phenotype [620]. Moreover, analysis of treatment-related changes in lipid composition in cancer cells may give clues about sensitivity to novel agents, and potential adaptive metabolic changes that may underpin treatment resistance [621].

With successive gains in instrument sensitivity currently being achieved, cell line-based lipidomics has extended to pathologically annotated clinical specimens. Several studies have analyzed lipids in surgical tumor tissue or in needle biopsies, either on homogenates of the samples or by mass spectrometry imaging. For example, Marien *et al.* discovered 91 differently expressed phospholipid species in tumor versus non-malignant tissue homogenates from 162 non-small cell lung cancer patients [44], while Wang *et al* recently identified tumor-related changes in the abundance of several lysophospholipid classes compared to matched normal mucosa in colorectal cancer patients [622]. GC-MS analysis of fatty acid content in 25 matched normal and tumor samples from colorectal cancer patients revealed reduced TAG and oleate (C18:1) in tumor tissues while total phospholipids, sphingomyelin, SFAs, PUFAs and cholesterol were increased [623]. Nagai *et al* studied 38 cases of hepatocellular carcinoma and identified the triacylglyceride TAG(16:0/18:1/20:1) as being more abundant in tumor compared to non-tumor tissues, while TAG(16:0/18:1/18:2) was more abundant in non-tumor tissue, both alterations being validated using DESI-MSI [624]. Budhu *et al* studied a total of 386 hepatocellular carcinomas, including paired normal and tumor samples from 30 patients, and by integrating metabolomic and transcriptomic data identified a signature of lipid changes indicative of enhanced SCD1 activity that was associated with more aggressive cancer [625]. Increasingly, discovery studies have been performed using MSI, and tumor-specific lipid profiles have been identified using MSI in a range of cancers (key studies summarized in Table 3). In some cases, there is evidence of the lipid profile being linked to histological or pathological subtypes of cancer. It is evident from inspection of the identified lipid classifiers that certain similarities in lipid profile exist between different cancers, such as tumor specific abundance of lyso-phospholipids and PI species, although in many cases the precise identity of these lipids should be interpreted with caution unless verified using tandem MS.

Although not standardly used in the clinic so far, the distinctive lipid profile of cancer tissue may have interesting applications as diagnostic biomarkers. As modern mass spectrometry imaging can be performed in minutes, tumor-characteristic lipid profiles may yield important information for clinical decision making in the operating theater [626]. In another setting, a special surgical knife is used (referred to as iKnife) that evaporates the tissue,

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which is analyzed in line and in real time by mass spectrometry using the REIMS technology, providing instant instructions to the surgeon. In some cases lipid profiles have been identified related to therapeutic response [627, 628], which raises the possibility that lipids may have useful prognostic value. Similarly, the MasSpec Pen identifies cancerous tissue in real time based on profiles of lipids, proteins and metabolites.

8 Lipids and lipid metabolism as promising tools and targets for anti-cancer therapies.

In view of the central role of lipids and altered lipid metabolism in the pathophysiology of cancer, the exploitation of lipid metabolism as a potential target for antineoplastic therapy has become a very active domain of research. Since the discovery of the overexpression and dysregulation of enzymes involved in lipid metabolism in cancer, various natural and synthetic compounds targeting lipid metabolism have been reported to be effective against cancer cells with a significant degree of selectivity. Much of the effort has focused on compounds targeting liquid acquisition, particularly *de novo* lipogenesis, with some compounds making it to clinical trials. One of the challenges of this approach is the context dependence of lipid acquisition and the high degree of plasticity of cancer cells, leading to the exploration of lipid uptake as an alternative or complementary target. One particularly promising antineoplastic strategy in this context exploits this plasticity in lipid acquisition to increase cellular lipid polyunsaturation to induce a unique vulnerability to ROS and to a variety of therapeutics that evoke changes in the redox balance as part of their mechanism of action. This strategy has been successfully employed in preclinical models to (re)sensitize cancers to chemo- and targeted therapies. Other approaches aim at disbalancing lipid homeostasis by interfering with specific lipid metabolism enzymes, inducing lipid toxicity. Besides targeting lipid metabolism, lipids themselves have also shown promise as anti-cancer lipid drugs, and as critical components of nanomedicines and lipid-based vehicles of therapeutics. Here we provide a short overview of some of the most promising or emerging therapeutic strategies based on lipids and altered lipid metabolism in tumors.

8.1 Cutting off lipid supplies

Based on the high dependence of many cancers on lipids, several approaches have been explored to cut off lipid supplies to cancer cells. As detailed above, cancer cells can acquire lipids through various routes, including *de novo* lipogenesis and lipid uptake.

Since the discovery of the overexpression of FASN in many cancers, this enzyme has been a prime target for anti-lipogenic drug discovery (Table 4). Initial studies with the fungal antibiotic cerulenin showed promising anti-proliferative and death-inducing effects in many cell lines, but suffered from the poor selectivity of this compound. Other natural compounds, including flavonoids such as quercitin, luteolin and EGCG found in green tea, were shown to block lipogenesis in cancer cells, along with their many potential mechanisms of action. Orlistat, an approved anti-obesity drug that reduces fat uptake from the gut by inhibiting lipases, has also been shown to inhibit FASN and to attenuate tumor growth in preclinical models. The first synthetic anti-FASN compound C75 showed potent effects in several preclinical models *in vivo*, but also produced severe side effects, including a dramatic weight

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loss caused in part by accumulation of malonyl-CoA and by a proposed role for FASN in neuronal stem cell functioning [629, 630]. Next generation compounds targeting FASN such as C93, IPI-9119 and TVB-2640 appeared less toxic and showed significant potential in various preclinical models. One of the compounds that has progressed most is TVB-2640 which is being explored for colon and other cancers in a phase I study and has entered phase II clinical trials for HER2 -positive BC in combination with paclitaxel and trastuzumab [285, 631, 632]. Interestingly, inhibition of FASN has also been shown to impair angiogenesis through mTOR malonylation [101].

Other enzymes of the pathway that have been explored as potential targets are ACACA and ACLY. Early studies on ACACA inhibition were performed with TOFA, which upon conversion to TOFyl-CoA (5-tetradecyloxy-2-furoyl-CoA) exerts an allosteric inhibition on ACACA. These studies showed promising results with induction of apoptosis in many cancer cell lines, but were blurred by its poor efficacy and the concomitant depletion of cellular CoA stores. The natural compound soraphen A, a myxobacterial metabolite, appears to be very efficacious in cell lines *in vitro*, even at nanomolar concentrations. Its death-inducing potential seems to depend on the abundance of exogenous lipids. The applicability of this compound is also limited by low bioavailability *in vivo*. Promising candidate drugs from the ND-600 series that were developed in the context of other metabolic diseases including dyslipidemia, steatosis, and obesity, have brought the targeting of ACACs in the cancer field closer to the clinic [633]. ND-646, a small molecule allosteric inhibitor of both ACACA and ACACB that prevents enzyme dimerization, has shown efficacy in preclinical models of non-small-cell lung cancer and breast and liver cancer and is in clinical trials [634]. As a dual inhibitor of both ACAC enzymes, the compound both inhibits lipogenesis and enhances FAO (*vide infra*). In this sense, ACAC and FASN inhibition may not be equivalent. FASN inhibition results in an accumulation of Malonyl Co-A which is the final product of the upstream enzyme ACACA, but is also a potent inhibitor of beta oxidation, and therefore FASN inhibition also blocks beta oxidation [103]. Conversely, ACAC inhibition may have the opposite effect, leading to a depletion of malonyl Co-A and may further drive beta oxidation. Inhibition of ACLY also attenuates tumor growth by regulating levels of acetyl-CoA, which feeds both FA and cholesterol synthesis. It also affects acetylation of proteins and subsequently evokes changes in gene expression.

The cholesterol synthesis pathway is another potential target. Notably, the use of statins, which inhibit cholesterol synthesis by targeting the rate-limiting HMG-CoA reductase enzyme and which are widely used as cholesterol lowering drugs, has been associated with a reduced risk of cancer development in animal models and in some, but not all cancers in human epidemiological studies. In a treatment setting, statin use has been associated with reduced mortality or recurrence in a wide range of cancers [635], although a recent meta-analysis of randomized trials in cancer showed no significant effect of adding statins to therapy on progression-free or overall survival [636, 637]. Moreover, re-analyses of large scale association studies on statin use have revealed low levels of evidence for a protective effect of statins on cancer incidence [638] or overall survival [637, 639]; emphasizing the need for larger, randomized Phase III trials in cancers where the strongest epidemiological data exists- although the feasibility of such studies is compromised by the current widespread use of statins for hypercholesterolemia in Western countries. Any enhanced

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outcome due to statin use may be in part be mediated by the reduction of circulating cholesterol and by changes in protein isoprenylation, which is also affected. In experimental studies, statins reduce the viability of cancer cell lines. Further evidence for cholesterol synthesis as a potential target comes from studies targeting the first enzymes committed to cholesterol synthesis i.e. squalene synthase.

A possible limitation of targeting lipid synthesis is that cancer cells may be able to compensate by increasing lipid uptake. However, it is conceivable that the kinetics of lipid uptake in a poorly vascularized tumor may be insufficient to fully compensate. Nevertheless, targeting lipid uptake has provided beneficial effects in a number of pre-clinical models. A challenge in targeting lipid uptake is that there are multiple mechanisms that may compensate for each other, including other receptors, endocytosis, or tunneling nanotubes [640]. One of the mechanisms that is shown to play critical roles in lipid uptake in several models and that shows promise as a therapeutic target is CD36. Targeting CD36 is shown to be a promising avenue in several preclinical studies in various cancer types including glioblastoma, melanoma and prostate cancer [159]. Most of these targeting approaches are based on TSP-1 mimetics. Some of these, such as ABT-510 have reached phase I and II clinical trials. It should be noted that interference with CD36 does not exclusively affect lipid uptake [641]. Several FABP inhibitors have been developed and tested for the prevention and treatment of obesity, atherosclerosis, diabetes, and metabolic syndromes. In cancer, most studies have used knockdown of FABP5, but recently the FABP5 inhibitors SBFI-102 and 103 have been shown to suppress prostate cancer growth and synergize with taxane-based chemotherapeutics [642]. On the other hand, activation of epidermal FABP (E-FABP) by EI-05 suppresses mammary tumor growth by promoting the anti-tumor activity of macrophages [643].

Targeting transcription factors as regulators of lipid metabolism may be another interesting approach. As detailed above, many cancers show an activation of SREBP-1 but targeting transcription factors such as SREBPs remains challenging. Fatostatin is an inhibitor of SREBPs that was originally developed to block insulin-induced adipogenesis [644]. This compound directly binds SCAP at a site distinct from the sterol-binding domain and hinders ER-to-Golgi transport of the SREBP-SCAP complex. Fatostatin: i) blocks hepatic lipid accumulation and body weight gain in obese mice; ii) inhibits cell growth by impeding intracellular shuttling in a SCAP-independent manner [645]; iii) has antiproliferative effects that are mediated via inhibition of mitotic microtubule spindle assembly [646]; iv) has shown to be a promising anticancer agent in BC (induced a significant reduction of several key genes in the cholesterol biosynthesis pathway including HMGCR and SQLE and blocked cell invasion in ER+ BC but not TNBC and specifically in LTED cells [416, 647], prostate (both AR-positive and metastatic AR-negative prostate cancer cells) [381, 648] and pancreatic cancer [649]. Blocking SREBP translocation with Fatostatin in prostate cancer cell: i) suppressed cell proliferation and anchorage-independent colony formation in both androgen-responsive LNCaP and androgen-insensitive C4–2B prostate cancer cells, ii) reduced *in vitro* invasion and migration in both cell lines causing G2/M cell cycle arrest, iii) induced apoptosis by increasing caspase-3/7 activity and cleavage of caspase-3 and PARP (Poly (ADP-Ribose) Polymerase), iv) significantly inhibited subcutaneous C4–2B tumor growth and markedly decreased serum PSA level compared to the control group *in vivo*

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animal results, v) decreased the expression of AR and its target gene PSA *in vitro* and *in vivo* [358, 381, 648].

Betulin is a natural compound abundant in birch bark that inhibits the maturation of SREBPs by directly interacting with SCAP and improves hyperlipidemia, insulin resistance and atherosclerotic plaques [650]. Betulin decreases hepatocarcinoma development and progression through reduction of SREBP-driven lipogenesis and attenuated inflammatory responses by down-regulation of tumor-promoting cytokines, including interleukin 6 (IL6), tumor necrosis factor alpha and IL1b [651]. Nelfinavir and its analogues block S2P cleavage leading to suppression of proteolytic activity and accumulation of SREBP1 precursor and ATF6 [652]. Nelfinavir induces liposarcoma apoptosis and is able to inhibit castration resistant prostate cancer cells proliferation *in vitro* [652, 653].

Silibin is a natural compound isolated from the seeds of milk thistle plant (Silybum marianum) and widely consumed as a hepatoprotective agent. Through activation of AMPK, SREBP1 phosphorylation is increased in turn inhibiting SREBP1 nuclear translocation. In this way, Silibin decreases nuclear protein levels of SREBP1 and their target genes in prostate cancer cells leading to reduced lipid and cholesterol accumulation with consequent cell cycle arrest and inhibition of tumor cell proliferation. Silibin also blocked androgen-induced lipid accumulation and prevented the development of androgen-independent LNCaP cell clones via targeting SREBP1 [654].Other agents targeting SREBP through activation of cAMP-PKA or AMPK signaling pathways [391] include i) indirect: Metformin, Thiazolidinediones, Resveratrol, and agonists of GLP1R, the cannabinoid receptor CB2R, and GPR119; and ii) direct: AICAR (5-aminoimidazole-4-carboxamide ribo-nucleotide), PT-1, S396 (inhibits the transcriptional activity of SREBP) (reviewed in [396]) and MT 63–78 [102]. Metformin has received significant attention due to epidemiological associations between its use as an anti-diabetic and cancer incidence and/or outcomes (reviewed in [635]), although better designed studies have now weakened associations with cancer risk [655]). Randomized trials of metformin with TK inhibitors in lung cancer have yielded conflicting results [656, 657], while no effects were seen in BC for randomized trials of metformin added to chemotherapy [658] or endocrine therapy [659]. The results of a number of ongoing Phase II randomized trials are now awaited to reveal the potential of metformin to improve cancer patient outcomes. Agonists of the cannabinoid receptor CB2R have shown preclinical efficacy against growth and/or invasion of cancer lines *in vitro* [660–665] and suppress *in vivo* tumor growth and metastasis [660, 661, 664], while MT 63–78 is showing promise as a specific and potent direct AMPK activator able to inhibit prostate cancer cell growth both in androgen sensitive and CRPC models, inducing mitotic arrest, and apoptosis [102].

Beyond SREBP, many studies have reported the *in vitro* and *in vivo* antiproliferative effect of LXR activation in all types of cancers [666], and PPAR-γ activation induces cell cycle arrest in several malignant cell lineages [667]. However, animal studies and clinical trials have not been conclusive on the beneficial effect of PPAR agonism as antineoplastic therapy [667]. Further attention to these equally important regulators of lipid metabolic genes may yield novel agents and combinatorial strategies.

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8.2 Blocking downstream lipid metabolism

Given the challenges outlined above in the targeting of transcription factors such as SREBPs and their upstream regulators, interest has also focused on directly targeting lipid metabolic enzymes themselves and, most notably, *de novo* lipogenesis via FASN. More recently, interest has broadened into inhibition of other key metabolic enzymes involved in synthesis, uptake and utilization of FAs. This has provided the opportunity not only to develop novel anticancer agents, but also to repurpose existing enzymatic inhibitors previously developed for metabolic disorders such as type II diabetes or hypercholesterolemia. Some promising new therapeutic targets are discussed below.

In the context of the cancer's plasticity in lipid acquisition, ACSLs may be interesting targets to block the use of FAs irrespective of whether they are synthesized *de novo* or acquired exogenously. Although ACSL enzymes are required for the assembly and storage of FAs, they play complex biological roles in physiology and cancer means that the context dependent contribution of their roles should be carefully considered. Specifically, whereas ACSL3 may be a good target in the context of lipid uptake dependent tumors, ACSL4 inhibition may be detrimental in helping to saturate cell membranes and protect cells from ROS stress.

Besides membrane phospholipids as a source of FAs, FAs can be assembled from neutral fat stores by the enzymes ATGL, HSL and MAGL [574]. ATGL in particular has been shown to have oncogenic roles in colorectal and lung cancer cells [575, 576], and may contribute to BC growth and invasiveness by releasing adipose derived FAs [577]. A pharmacological inhibitor of ATGL is available [578]. Inhibition of MAGL by the small molecule JZL184 suppresses tumorigenesis of melanoma and ovarian cancer cells [581]. ATGL knockdown or chemical inhibitor such as atglistatin suppresses the growth of several types of cancer cells, although ATGL expression in human malignancies is lower than in adjacent normal tissues. Inhibitors (JZL184) or shRNA probes that target MAGL can impair prostate cancer cell aggressiveness.

Knockdown or chemical inhibition of SCD1 shows promising efficacy and treatment sensitization in a range of cancers [206–209], while inhibition of one or both FADS enzymes has shown preclinical efficacy in intestinal cancer [217]. Whereas the role of FA and membrane lipid desaturation in cancer is well-described, and novel agents are available that are currently being evaluated in preclinical cancer models (see Section 4.3), comparatively less progress has been made in targeting of membrane lipid elongation in cancer. However, as described in section 4.4, membrane lipid elongation is a common feature of many cancers. The main limitation of ELOVL targeting in cancer is a current lack of development of small molecule inhibitors, further complicated by the membrane-bound structure of the ELOVL enzymes. Nevertheless, inhibitors of ELOVL6 have been synthesized [668–672], some of which show cross-selectivity for ELOVL3, although these have not yet been studied for their anticancer properties. Hyperlipidemic agents bezafibril and gemfibrazil have been reported to inhibit ELOVL1 [673], but it would be difficult to mechanistically separate their effects on ELOVL1 from their effects on cholesterol and other lipids in any preclinical investigations. Overcoming the technical challenges of crystallizing and developing inhibitors of this intriguing enzyme family will allow selective inhibition of different

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elongation pathways in cancer cells, which will provide insight into the relative significance of each pathway and its various lipid products for tumorigenesis and metastasis.

Pharmacological inhibition of FAO using the CPT1 inhibitor etomoxir or perhexiline not only reveals single agent efficacy in cancer cell lines [674–678], but also sensitizes tumor cells to chemotherapy [149, 246, 247, 679], radiotherapy [680, 681] and endocrine therapies [682]. Notwithstanding the fact that at least some of the anticancer properties of etomoxir occur via non-CPT1A-related mechanisms [683], these reports highlight the importance of FAO not only for cancer cell survival, but also as a key mechanism of resistance to therapy.

FABP modulators include derivatives of niacin, quinoxaline, arylquinoline, and bicyclicpyridine. They modulate the interaction of FAs with FABPs and can have dual effects in a context dependent manner. For example, an activator of epidermal FA binding protein, EI-05, suppresses mammary tumor growth in mice [643], while inhibitors of FABP-5 are active alone or can synergize with taxanes to inhibit prostate tumor growth in mice [642].

Constitutive activation of choline kinase is a key metabolic feature of oncogene-driven cancers, resulting in increased cellular phosphocholine levels. A range of choline kinase inhibitors have been developed since the 1990s, and exhibit antiproliferative activity in cancer cells [684–688], however none have yet been investigated clinically.

Lipidation of oncoproteins presents a novel vulnerability for cancer therapy, as this post-translational modification can stabilize or activate a range of cancer cells [281]. Farnesylation in particular has experienced a strong focus for drug development in cardiovascular disease, and novel clinical agents (e.g. tipifarnib, lonafarnib, BMS-2154662) have recently been repurposed for cancer in a series of Phase I/II studies evaluating combinatorial efficacy, with promising results. Palmitoylation has been targeted using a preclinical agent, 2-bromopalmitate, which has demonstrated sensitization of osteosarcoma cells to the chemotherapeutic agent adriamycin [689] and revealed an intriguing role for palmitoylation of PD-L1 in enhancing its stability, with 2-bromopalmitate enhancing T-cell immune responses in colon and breast tumor models [690, 691]. Given the increasing interest in harnessing immunometabolism for cancer therapy, these agents afford an exciting new approach to immunotherapy beyond the current anti-PD-L1 antibody approaches.

8.3 Targeting lipid metabolism in combinatorial approaches as sensitizer to other therapies

A plethora of evidence points towards the contribution of lipid metabolism to multiple aspects of cancer. Although the contributions of blunt approaches such as blocking lipogenesis or lipid uptake have translational effects in preclinical models, they generally exert a cytostatic effect or reduce the metastatic disease burden, but they are not curative. A more rational and less complex approach is to exploit context and tissue dependent vulnerabilities acquired by cancer cells. In this way, the magnitude of the sum of multiple combined approaches that exploits acquired vulnerabilities is many times greater than the contribution of each separate approach. The concept of such approaches often termed ‘synthetic lethality’ is certainly not unique to metabolism, but may be particularly applicable

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to it, as in contrast to degenerate signaling pathways, lipid metabolic pathways often converge on a few key enzymes. Therefore, if a lipid metabolic pathway becomes less dispensable, it can be a potent antineoplastic target. For example, in a particularly lipid deficient environment such as in a solid tumor, lipogenesis will be required to generate membrane biomass, whereas in a lipid rich environment such as that of primary breast and prostate cancers, targeting lipid uptake may be more prudent. Combinatorial approaches in targeting lipid metabolism in cancer, often combined with standard of care therapies, is emerging as an immensely fruitful field in translational research.

The intimate link between growth factor and oncogenic signaling and lipogenesis is well-established, as cell proliferation requires the generation of biological membranes. Castration resistant metastatic prostate cancer re-activates endogenous androgen receptor signaling, and moreover rapidly develops resistance to antiandrogen compounds, often through amplification of the androgen receptor gene or the generation of novel splice variants such as the ARV7. Importantly, the androgen receptor promotes a program of SREBP-dependent lipogenesis, which contributes to therapy resistance to antiandrogens, whereby a combination of anti-androgens and FASN inhibition synergistically reduce disease burden [103]. Similarly, in liver cancer cells the combination of AMPK mediated ACACA inhibition synergizes with antiangiogenetic therapy, with a possible mechanism being that under a hypoxic and nutrient deprived setting, lipogenesis becomes increasingly critical in promoting cell proliferation [692]. In both these examples, the combinatorial approaches include an addition over the standard of care, allowing more rapid clinical adoption. In addition to the role of oncogenes and growth factor receptors in promoting lipogenesis to power membrane biogenesis, lipogenesis may in turn power oncogenic signaling. FASN mediated lipogenesis contributes to HER2 expression and clustering, and in turn the combined inhibition of HER2 and FASN induces apoptosis in BC cell lines *in vitro* [693]. Similarly, ELOVL2 mediated enrichment of PUFA containing membrane PL species promotes EGFR signaling in glioma, and the combination of ELOVL2 KO and anti-EGFR therapy exerts a dramatic antineoplastic effect [224]. This is further supported by a study in lung cancer showing that SREBP mediated changes to membrane fluidity promote EGFR phosphorylation and combined inhibition of SREBP and EGFR shows translational benefit [694]. Menendez and Lupu show that FASN regulates E2/ERα signaling in BC cells. Inhibition of FASN activity induced reduction of ERα protein, suppression of E2-stimulated BC cell proliferation and inactivation of AKT mediating E2-promoted anchorage-independent colony formation. Furthermore, treating BC cells with pure antiestrogen or inhibitor of MEK/ERK, blocked the interaction between FASN blockade and E2-stimulated ERα transactivation [695].

In tumors that are surrounded by a lipid rich environment, lipid uptake may play a dominant role over lipogenesis in establishing a similar phenotype. Although inhibiting lipid uptake remains challenging, combinatorial approaches for inhibiting CD36 mediated lipid uptake have been met with some success in preclinical models. In HER2 positive therapy resistant models, CD36 deletion can re-sensitize cancer cells to lapatinib [158]. Several lines of evidence point towards the context dependent requirement of FAO under conditions of increased lipid uptake. In non-solid leukemia cells which do not suffer from the drawback of a nutrient deficient environment, the oxidation of exogenous FAs drives energy generation.

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Leukemia cells are therefore sensitive to the combination of beta oxidation inhibitors and apoptosis inducers [696]. In melanoma cells, anti-MAP kinase therapy inhibits lipogenesis and kills the majority of melanoma cells, however a small subset of persister cells survive, and they in turn require CD36 mediated lipid uptake to drive beta oxidation. Combinatorial inhibition of beta oxidation and MAP Kinase inhibition significantly attenuated the ability of cells to develop therapy resistance [697].

Lipogenesis inhibition sensitizes lung cancer cells to carboplatin [634, 698]. The fact that several tumor types are sensitized to cytotoxic chemotherapy in combination with lipogenesis inhibitors hints at roles for lipids other than membrane biogenesis and energy production. A study showed that inhibition of lipogenesis promotes membrane lipid poly-unsaturation mediated by lipid uptake, and this in turn confers a sensitivity to ROS inducing agents such as chemotherapeutics [15]. Since this publication, further evidence supporting this claim has come to light. In BRAF mutant melanoma models, therapy resistance depends on sustained lipogenesis mediated by SREBP activity. Inhibition of SREBP by SCAP targeting compounds betulin or fatostatin drive membrane lipid poly-unsaturation and confer sensitivity to ROS elevation in melanoma. The combination of SREBP inhibition synergizes with BRAF inhibition to elevate ROS, and exerts a potent antineoplastic effect in therapy resistant melanoma [16, 699].

Besides chemotherapy, radiotherapy is an often-critical early therapeutic step in cancer treatment, and much like chemotherapy, its cytotoxic effects are in part mediated by ROS. Concordantly, the combination of radiotherapy and lipogenesis inhibition synergistically decreased tumor growth in mouse models of prostate cancer [700]. Recently, it is shown that under ionizing radiation, cancer cells increase the expression of ACSL4 which can act as a potent inducer of ferroptosis. Moreover, radiotherapy combined with ferroptosis inducers led to the radio-sensitization of cancer cells [701, 702]. Promisingly, radiotherapy can work in concert with immunotherapy to sensitize tumor cells to ferroptosis, and effect that can be further enhanced by ferroptosis inducers [703].

8.4 Dietary intervention of cancer

Since many cancers have the ability to take up lipids and since excessive caloric intake and obesity are associated with cancer aggressiveness, reoccurrence and resistance to therapy, diet adjustments could have significant benefits in some types of cancer. In a BRAF V600E mutant melanoma xenograft model in mice, a high fat diet resulted in enhanced tumor growth, while overall survival and response to dacarbazine in obese melanoma bearing mice could be improved by weight control intervention [704, 705]. Conversely, in so called ketogenic diets, which are high in fat but low in carbohydrates with an overall normal caloric intake, several studies have described anti-cancer effects such as reducing the growth of a glioblastoma PDX model [706] or sensitizing tumors to targeted therapies [707, 708]. These studies suggest that beyond the total lipid levels in the diet, the total caloric intake and the lipid composition of the diet play an important role.

Whereas saturated fat overall has been shown to increase the risk of several cancers, MUFA have been reported to be protective. Particularly olive oil appears to be effective in several studies [709, 710]. These effects may not be entirely attributed to its high content of

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MUFAs, but also its high content of lipid-soluble antioxidants such as alpha-tocopherol, which protects against free radical-induced lipid peroxidation [711]. High intake of omega-6 PUFAs has been linked with a poor outcome in cancer patients, whereas omega-3 lipids appear to ameliorate cancer. Multiple mechanisms have been reported, including a differential effect on the production of prostaglandins and other eicosanoids [712, 713]. Several studies have reported that supplementation of conjugated linoleic acid (CLA), can protect against cancer in animal models of chemical carcinogenesis [714]. CLA is thought to modulate prostaglandin metabolism, to affects growth factor signaling, activation of PPARs-alpha and several other mechanisms. Interestingly, a proof of principal biomarker study of CLA administration to newly-diagnosed BC patients showed encouraging results [715]. In view of the well-known role of eicosanoids and other oxylipins in the communication with the immune component, it will be interesting to see to what extent modulation of lipid composition by the diet affects the outcome of immunotherapy as a rapidly expanding therapy option for many cancers.

8.5 Transdifferentiation of cancer cells by modulating lipid metabolism

Another interesting therapeutic approach based on the modulation of lipid metabolism involves the transdifferentiation of cancer cells into fat cells. This concept has been proposed for cancer stem cell transdifferentiation by treating them with specific unsaturated FAs [716]. Recently, a similar strategy has been proposed to exploit the plasticity of cancer cells to undergo endothelial-mesenchymal transition to force them to transdifferentiate into post-mitotic adipocytes, thereby blocking primary tumor invasion and metastasis. In preclinical BC model systems this was achieved by a combination treatment with the antidiabetic drug rosiglitazone (a PPAR agonist) and inhibitors of MEK [717].

8.6 Anti-cancer lipid drugs

Since the 1970's several synthetic lipids, mainly alkylphospholipids, have been shown to be effective towards several diseases, including cancer. These molecules resemble natural ether lipids and thus lack ester bonds, making them more resistant to the degradation by lipases. Alkylphospholipids incorporate into the cell membrane and exert their effects in part by targeting lipid microdomains, membrane disorganization and changes in signaling of specific proteins. Several alkylphospholipids are currently in clinical use, such as miltefosine, edelfosine and perifosine. In the context of cancer, edelfosine has been studied in a variety of tumor types. In cell line models, edelfosine inhibits survival pathways such as MAPK/ERK and Akt/PKB pathways and activates the Fas/CD95cell death receptor, and shows significant selectivity towards cancer cells. In animal models, edelfosine showed a higher accumulation in cancer tissues and was active against several cancer types. In phase I and II clinical trials, edelfosine was shown to be safe and possibly effective. Recently, alkylphospholipids such as edelfosine have been tested as conjugations with other drugs targeting lipid metabolism, including quercitin, and are being exploited in nanoassemblies with chemotherapeutics as nanomedicines (*vide infra*) [718]. Several other synthetic lipids have been tested in cancer models including minerval, a synthetic 2-hydroxyoleic acid (2OHOA) and propofol-DHA [719].

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8.7 Lipid-directed drug targeting approaches in cancer

The differential lipid composition of cancer cells can also be exploited to target drugs to cancer cells. One of these strategies exploits the externalization of phosphatidylserine (PS) to the surface of cancer cells. Both *in vitro* and *in vivo*, it was shown that specific nanovesicles containing saposin C specifically target tumor cells by recognizing PS on the cell surface [720]. Tumor targeting is further enhanced by the fact that the affinity of saponin C for PS is the highest at acidic pH, this way exploiting the acidic microenvironment of tumors. Other approaches involve the targeting of PE by compounds such as duramycin, cinnamycin, cyclotides and ophiobolin A.

8.8 Lipid-based drug delivery systems for cancer therapeutics

Due to tumor-specific constraints including poor vascularization and high interstitial pressure, efficient drug delivery into tumors has remained a challenge. Lipid-based vesicles, including liposomes, microbubbles or nanoparticles have long been explored as carriers for therapeutics. Because of their ability to 'shield' toxic compounds, their small size favoring tissue penetration, high payload, long retention times and efficient uptake by cancer cells, lipid-based or lipoprotein-based vehicles are increasingly studied as drug delivery systems, with major advances in the last few years. Some of these carriers exploit the unique natural properties of lipoprotein particles, including their binding to lipoprotein receptors, which are frequently overexpressed in cancer cells to support lipid take up (*vide supra*). They are internalized through receptor-mediated mechanisms, upon which the therapeutic load is released, depending on the nature of the vehicle. Both natural and recombinant LDL-and HDL-derived particles and phospholipid-based nanovectors and nanodiscs, of which the lipid composition can be modulated, are being explored in combination with diverse groups of therapeutic agents such as chemotherapeutics (paclitaxel, hydroxycamptothecin), imaging agents, radioactive compounds, photodynamic agents, nucleic acids including siRNAs, proteins and carbohydrate complexes [721]. Currently some 50 nanoparticles are FDA approved including some for the treatment of cancer [722].

New players on the block are extracellular vesicles (EVs), which are derived from cells. As they are natural, they are thought to be less susceptible to the host immune system than artificial nanoparticles. Using various physical and chemical methods, EVs can be loaded with cancer drugs or other cancer targeting agents. Their surface can be decorated with specific homing peptides to enhance selective uptake by target cells through direct fusion with plasma membrane or through endocytosis pathways [723, 724]. The implementation of EVs as lipid-based drug delivery systems awaits however further preclinical developments, including maximization of drug loading, more selective targeting and optimization of large scale production and purification, and achieving safety requirements by FDA and EMA (reviewed in [725]).

9 Future perspectives

Although a link between lipids and cancer has been known for decades, recent years have witnessed an explosion of new findings portraying a complex and intricate network of alterations in lipid metabolism in cancer that involves nearly every lipid-related pathway and

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biological function. Recent advances in lipid analysis technologies predict that our current knowledge represents only the tip of the iceberg. Current lipidomics approaches cover only a small fraction of the more than 200,000 predicted lipid species. Many less abundant lipid species remain under the radar, yet may play important roles for instance in the intricate interplay between cancer and immune cells. In this context, recent developments in ionization methods including MALDI-2 and their application for instance in redox lipidomics, provide an exciting opportunity to study rare lipids [726, 727]. In view of the ongoing shift in cancer research towards single cell approaches revealing the importance of tissue heterogeneity in cancer progression and therapeutic outcome, we will witness a shift in the lipidomics field from lipidomics analyses on bulk tissue to single cell and spatial analysis by mass spectrometry imaging. New technological developments in this domain promise an unseen performance in terms of analytical aspects as well as spatial resolution, leading to novel insights in the role of lipids in the complex metabolic interplay between different cell types in the heterogenous tumor microenvironment. With novel technologies allowing imaging of lipids at the intracellular level including dynamic SIMS ion microcopy and Raman microscopy, a whole new area of lipid research is opening up, revealing changes in organellar lipidomes, trafficking pathways and membrane structures [728, 729]. The further development of stable isotope lipidomics will allow to follow changes in pathway fluxes instead of current steady state analysis and together with spatial multi-omics approaches will provide unprecedented insight in affected pathways and potential biomarkers. Along with these developments there is an urgent need for standardization of methods and technologies to allow future clinical implementations of the discovered biomarkers. In terms of therapeutic potential, current findings suggest that interference with lipid metabolism will have promising applications, particularly in combinatorial approaches[16]. With small molecules targeting enzymes in lipid metabolism entering clinical trials we are at the doorstep of witnessing the clinical exploitation of altered lipid metabolism as a hallmark of cancer. The link with the diet, including dietary lipids will also create unique opportunities for preventive strategies and therapy enhancement. Particularly in the field of tumor immunology, lipids hold great potential as modulators. In summary, although lagging behind compared to other omics approaches, the study of lipids in cancer is rapidly catching up and is establishing itself as a central hallmark of cancer with promising opportunities for clinical application.

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Abbreviations

AA	arachidonic acid
ACACA	acetyl-CoA carboxylase alpha

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ACACB	acetyl-CoA carboxylase beta
ACLY	ATP-citrate lyase
ACSL	Acyl-CoA Synthetase
APT	acylprotein thioesterase
AR	androgen receptor
ASM	acid sphingomyelinase
ATGL	adipose triglyceride lipase
ATX	autotaxin
BC	breast cancer
ccRCC	clear cell renal cell carcinoma
CE	cholesteryl ester
ChoKα	Choline kinase alpha
CM	chylomicron
CoA	co-enzyme A
CPT	carnitine palmitoyl transferase
DAG	diacylglycerol
EGFR	epidermal growth factor receptor
ELOVLs	fatty acid elongases
EPA	eicosapentaenoic acid
ER	endoplasmic reticulum
ER+/−	estrogen receptor positive/negative
ESI	electrospray ionization
FA	fatty acid
FA2H	fatty acid 2-hydroxylase
FABP	fatty acid binding protein
FADS	fatty acid desturase
FAO	fatty acid oxidation
FASN	fatty acid synthase
FDG	fluoro-deoxy glucose

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FFA	free fatty acid
GBM	glioblastoma multiforme
GPIHBP1	glycosylphosphatidylinositol high density lipoprotein binding protein 1
HPLC	high performance liquid chromatography
HSL	Hormone sensitive lipase
HSPG	heparan sulfate proteoglycan
INSIG	insulin-induced gene
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LPA	lysophosphatidic acid
LPAR	LysoPA receptor
LPCAT	lysophosphatidylcholine acyl transferase
LPL	Lipoprotein Lipase
LysoPA	lysophosphatidic acid
LysoPC	lysophosphatidylcholine
LysoPL	lysophospholipid
LXR	Liver X receptor
MAGL	monoacylglycerol lipase
MALDI	matrix-assisted laser desorption/ionization
MAPK	Mitogen-Activated Protein Kinase
MUFA	monounsaturated fatty acid
MS	mass spectrometry
MSI	mass spectrometry imaging
PA	phosphatidic acid
PAP	phosphatidic acid phosphatase
PAT	palmitoyl S-acyltransferase
PC	phosphatidylcholine
PDC	pyruvate dehydrogenase complex

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PE	phosphatidylethanolamine
PET	positron emission tomography
PGE_2	prostaglandin E2
PI	phosphatidylinositol
PL	phospholipid
PKC	protein kinase C
PLA/C/D	phospholipase A, C or D
PLSCR	phospholipid scramblase
PPAR	peroxisome proliferator-activated receptor
PS	phosphatidylserine
PTEN	Phosphatase and Tensin homolog
PUFA	polyunsaturated fatty acid
ROS	reactive oxygen species
RXR	retinoid X receptor
S1P	sphingosine-1-phosphate
SCAP	SREBP cleavage-activating protein
SERM	selective estrogen receptor modulator
SFA	saturated fatty acid
SCD	stearoyl-CoA desaturase
SREBP	sterol regulatory element-binding protein
TAMs	tumor-associated macrophages
TF	transcription factor
TAG	triacylglyceride
TNBC	triple-negative breast cancer
VLDL	very low-density lipoprotein
VLDLR	very low-density lipoprotein receptor

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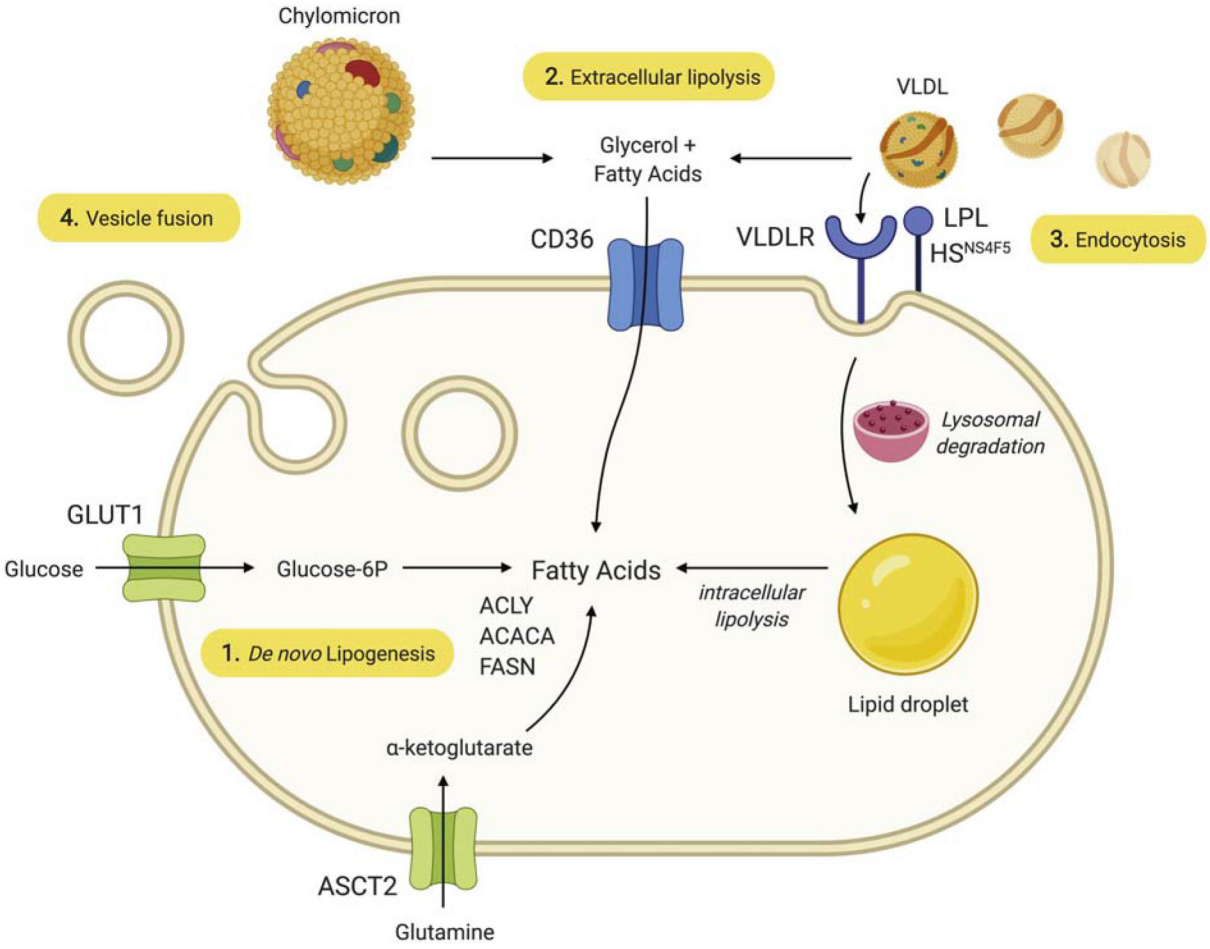

Figure 1: Currently recognized mechanisms of lipid acquisition by cancer cells.

1) FA may be synthesized *de novo* using ATP citrate lyase (ACLY), acetyl-CoA carboxylase-α (ACACA), and fatty acid synthase (FASN). 2) FFA derived from the circulation or from local LPL-mediated extracellular lipolysis of TAG carried in lipoproteins such as VLDL enter the cell through CD36. 3) Alternatively, VLDL may dock on LPL that is bound to the cell surface heparan sulfate proteoglycan motif HS^{NS4F5}, which optimizes positioning of the VLDL for endocytosis using the VLDL receptor (VLDLR). In this case, TAG are hydrolyzed intracellularly. Cholesterol-rich LDL particles may be similarly endocytosed using the LDL receptor without participation of LPL or HS^{NS4F5} (not shown). 4) Lipids and other molecules carried in exosomal vesicles may enter the cell through fusion with the plasma membrane.

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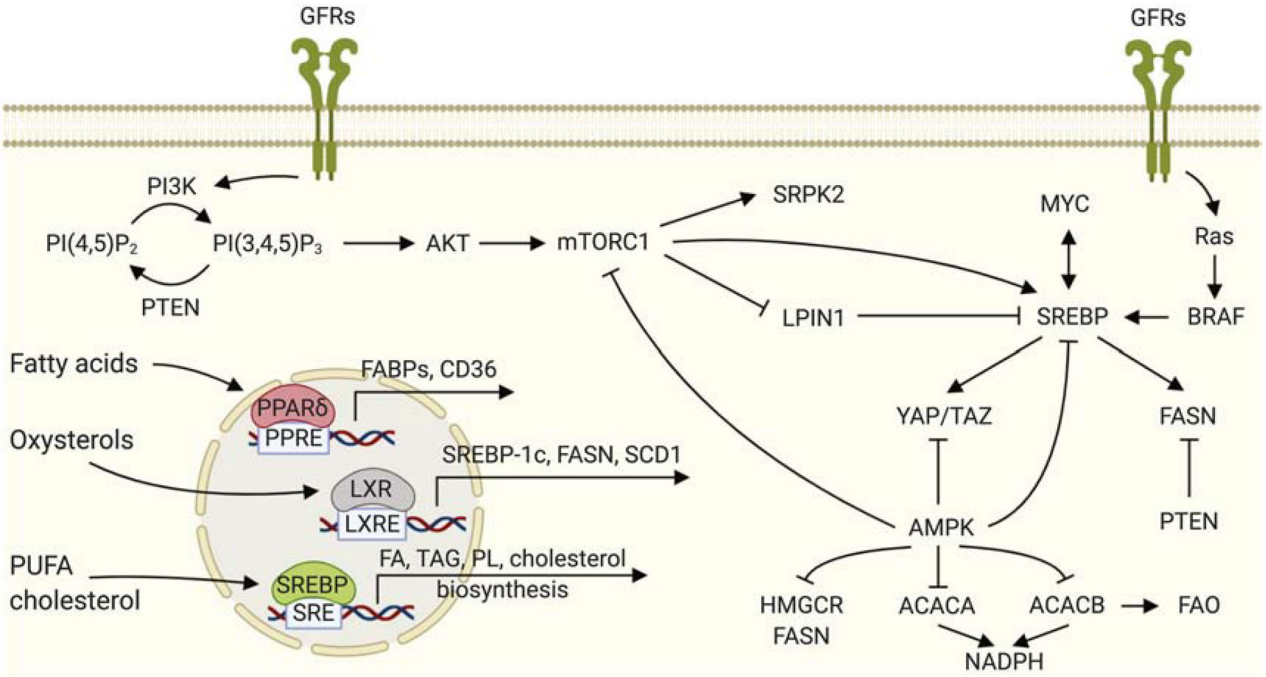

Figure 2: Key drivers of alterations in lipid metabolism

Cellular FA and cholesterol acquisition and metabolism are transcriptionally controlled and tightly regulated by Liver X Receptors (LXR) and Peroxisome Proliferator-Activated Receptors (PPARs) and by the basic-helix-loop-helix-leucine zipper (bHLH-LZ) transcription factors (TF) Sterol Regulatory Element Binding Proteins (SREBP). Multiple growth factor receptors (GFRs) regulate lipid metabolism through the PI3K/AKT/mTORC1 and MAPK signaling axes. SREBP and its downstream targets such as FASN and ACACA are regulated by a multitude of signaling molecules, including AMPK, MYC, PTEN and BRAF.

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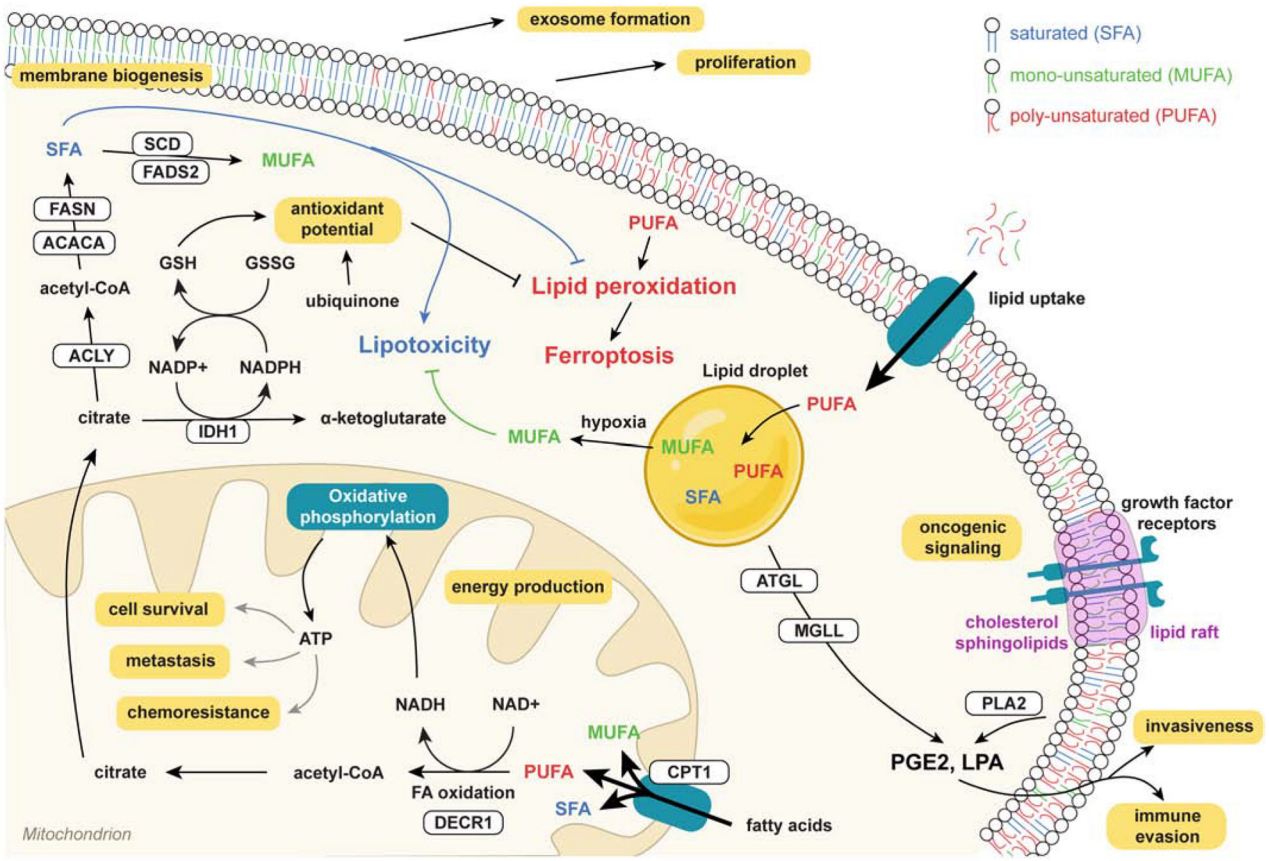

Figure 3: Lipids as central players in cancer biology.

Main mechanisms by which lipids contribute to cancer biology. FA synthesis and uptake support membrane biogenesis to drive cell proliferation and exosome formation. However, since increased SFA levels induce lipotoxicity, desaturation to MUFA is required. As membrane-incorporated PUFA is prone to lipid peroxidation and underlies ferroptotic cell death, multiple mechanisms can be deployed to reduce relative PUFA abundance in the membrane. By increasing lipogenesis, relative SFA and MUFA levels are increased, decreasing relative PUFA levels. Furthermore, PUFAs can be stored in lipid droplets or catabolized through FAO. Besides generating ATP to drive cell survival, metastasis and chemoresistance, FAO can increase the antioxidant potential through GSH synthesis, further offering protection against lipid peroxidaton and ferroptotic cell death. Finally, lipids play crucial roles in cellular and intracellular signaling through regulation of membrane fluidity and lipid rafts, and the synthesis of lipid-derived mediators regulating important aspects in tumor biology such as immune evasion and cellular invasion.

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Table 1:

Lipidomic studies on biofluids reporting diagnostic lipid signatures

Cancer type	Control samples	Cancer samples	MS Platform	Biofluid	Lipids altered	Reference
Ovarian	212	211	LC/ESI/MS/MS	Plasma	PPE(16:0,18:1) LPC15:0 LPA18:2 PPE(18:0,22:6)	Shan et al, 2012 [1]
Liver	90	82	UPLC-MS	Serum	LPC16:0 LPC18:0 PS16:0 PC18:0	Wang et al, 2012 [2]
Liver	37	37	GC-MS	Plasma	18:2n-6 18:1n-9 20:4n-6 16:0	Qiu et al, 2015 [3]
Lung	495	58	FTICR-MS	Serum	SM(16:0,16:1) LPC18:1 LPC20:4 LPC20:3 LPC22:6	Guo et al, 2012 [4]
Lung	147	199	ESI-MS	Plasma	LPE18:1 CE18:2 ePE40:4 SM22:0	Yu et al, 2017 [5]
Prostate	76	57	Q-TOF-MS	Plasma	ePC38:5 PC40:3 PC42:4	Patel et al, 2014 [6]
Breast	74 (inc. 40 non-malignant lesions)	40	GC-MS	Serum	16:0 18:0 18:2 18:3 20:5 22:5	Lv et al, 2012 [7]
Colorectal	84	63	GC-MS	Plasma	10:0	Crotti et al, 2016 [8]

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Table 2:

Lipidomic studies reporting prognostic lipid signatures in biofluids

Cancer type	Samples	Outcome	MS	biofluid	Lipids altered	Reference
		Measure	Platform			
Lung	300 Pre-treatment	Risk of cancer development	LC//MS	Plasma	Shingosine 1-phosphate	Alberg et al, 2013 [9]
Prostate	3,057 Matched case-controls (EPIC study)	Development of advanced or aggressive prostate cancer	MS)	Plasma	PCs, lysoPCs	Schmidt et al, 2020 [10]
Hepatocellular carcinoma	43	Responders vs non-responders to sorafenib	RPLC-MS	Plasma	PC34:2; PC34:3; PC35:2; PC36:4a; PC34:3e; acylcarnitine (18:0); cholesterol ester (20:2); DG34:2	Saito et al, 2018 [11]
Ovarian	101	Recurrence vs non-recurrence following standard of care therapy	UPLC-MS	plasma	31 lipids predicted recurrence; LPG20:5 increased predictive power of current clinical predictors; reduced triacylglycerides predicted early relapse	Li et al, 2017 [12]
Prostate	159	Overall survival	LC-MS/MS	plasma	Cer (d18:1/24:1); SM(d18:2/16:0); PC(16:0/16:0)	Lin et al, 2017 [13]

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Table 3:

Overview of MSI based lipidomics studies

Cancer type	Samples	MS Platform	Main observations	Ref.
Bladder cancer	20 tumors, 20 benign	DESI-MS	PS(18:0/18:1) and PI(18:0/20:4) upregulated in tumor tissue	[14]
Brain cancer	36	DESI-MSI	Lipid signatures varied between subtypes of glioma, PI(18:0/20:4) and PS(18:0/22:4) were the most significant discriminatory lipids	[15]
Breast cancer	28	MALDI-TOF/TOF	Cancerous regions enriched in mono-unsaturated PC species versus saturated	[16]
Breast cancer	8	MALDI-TOF/MS	A complex signature of +/− 20 PC and TAG species differentiates cancer from normal.	[17]
Breast cancer	56	MALDI-iMScope	Two different populations of cancer cells that predominantly expressed either PI(18:0/18:1) or PI(18:0/20:3).	[18]
Breast cancer	67 Tumors, 55 containing matched benign	DESI-MSI	Highly saturated lipids could distinguish breast cancer from benign tissue. Distinct lipid profiles were evident across different molecular tumor subtypes, and PE38:6 and PS38:3 plus 2 fatty acids were able to distinguish ductal carcinoma in situ from invasive breast cancer	[19]
Breast cancer	86 invasive tumors, 45 normal tissue	DESI-MSI	Complex signature of >40 lipid masses could distinguish cancer from normal, and was validated in two independent centers	[20]
Colorectal cancer	Training: 12 Validation: 40	MALDI-TOF/TOF	Lipid signature correlates with prognosis	[21]
Colorectal cancer	12 tumors, 12 matched benign tissue	MALDI-MSI	Cancerous tissues had higher levels of PC(16:0/18:1), lysoPC(16:0) and lysoPC(18:1) compared to matched normal tissue	[22]
Gastric cancer	62	DESI-MSI	Lipid signatures distinguished gastric cancer from normal tissue, and were validated on surgical margin samples	[23]
Lung adenocarcinoma	25	LC-MS + MALDI-iMScope	Enriched monounsaturated/saturated PC ratios in cancerous regions	[24]
Oral cancer	Training: 3 Validation: 1	MALDI-TOF/TOF	Logistic regression classifier allowed for a high precision labeling of cancerous regions	[25]
Ovarian cancer	107	DESI-MSI	Lipid profiles were tissue type-dependent. PA, PS, PE, PG and ceramide species were discriminatory for cancer versus normal.	[26]
Medulloblastoma + Pineoblastoma	MB: 8 PB: 3	MALDI-FTMS	Glycerophosphoglycerols and sphingolipids allow differentiation between MB and PB	[27]
Prostate cancer	10	MALDI-FTMS	31 lipids correlated with Gleason score	[28]
Prostate cancer	52	MALDI-IMS	Cancerous tissues had higher levels of PI species (PI(18:0/18:1), PI(18:0/20:3), PI(18:0/20:2)	[29]
Prostate cancer	31	MALDI-IMS	Decreased levels of lyso PC (16:0/OH) and SM(d18:1/16:0) in tumor vs benign regions of tissues; lower tumoral lysoPC(16:0/OH) levels were associated with biochemical relapse	[30]
Prostate cancer	18	DESI-MSI	Benign tissue regions had higher levels of lysoPEs, PI and citrate; Malignant regions had higher levels of FAs, PE, PC, PI and glutamate	[31]
Prostate cancer	68	DESI-MSI	Cholesterol sulfate was higher in malignant and pre-malignant lesions compared to benign tissue	[32]
Non-small cell lung cancer	Discovery: 73 Validation: 89	ESI-MS/MS + MALDI-FTMS	40 and 42 carbon PC and PE species enriched in cancerous regions; decrease in SM and specific PI	[33]
Renal cell cancers	20 normal 15 benign 46 tumors	DESI-MSI	Lipid profiles could distinguish normal kidney from benign neoplasms and different subtypes of cancer, increased cardiolipins were prominent features	[34]

Cancer type	Samples	MS Platform	Main observations	Ref.
Skin cancer (basal cell carcinoma)	86	DESI-MSI	PG(18:1/18:1), PS(18:0/20:4), PI(16:1/18:0) and PI(18:2/18:0) more abundant in carcinoma versus normal skin; cholesterol sulfate was higher in normal compared with tumor tissue	[35]

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Table 4:

Overview of potential agents as modulators of lipid metabolism in cancer

Target	Agent	Phase of Development	Comments	Reference
FASN	Orlistat	Approved	Antiobesity lipase and FASN inhibitor; not yet assessed clinically for cancer	[36, 37]
	cerulenin	Preclinical		[37, 38]
	C75	Preclinical		[580, 581][37, 38]
	C93	Preclinical		[39]
	IPI-9119	Preclinical		[40]
	TVB-2640	Phase II	Trials in breast cancer +/− trastuzumab/docetaxel	[41–43]
	Fasnall	Preclinical		[44]
ACACA	TOFA	Preclinical		[45–47]
	Soraphen A	Preclinical		[48]
	ND-646	Preclinical		[49, 50]
HMGCR	Statins	Approved	Association studies between statin use and outcomes in many cancers, some randomized trials	[51–54]
CD36	ABT-510	Phase I	Trial in metastatic melanoma	[55]
SREBPs	Fatostatin	Preclinical		[56–59] [60, 61] [62]
	Betulin	Prelinical		[63–65]
	Sibilin (milk thistle)	Clinical	Nutritional supplement in trials for improvement of toxicity/ quality of life in acute lymphoblastic leukemia, head and neck cancer and BC	[66–68]
AMPK	MT 63–78	Preclinical		[69]
	JWH-133	Preclinical	CB2R agonist	[70–75]
	GPR119 agonists (GSK1292263; MBX-2982)	Phase I/II for T2DM	Preclinical studies in cancer	[76, 77]
	Metformin	Approved for T2DM	Randomized clinical studies in lung and breast cancer	[78–81]
	AICAR	Approved for T2DM	Preclinical studies in cancer	[82, 83]
LXR	LXR-623	Phase I for atherosclerosis	Preclinical studies in cancer	[84]
ACSLs	Triacsin C	Preclinical		
ATGL	atglistatin		Specific for murine ATGL	[85]
MAGL	JZL184	Preclinical		[86]
SCD	A939572	Preclinical		[87–89]
	T-3764518	Preclinical		[90, 91]
	SSI-4	Preclinical		[92]
	SW203668	Preclinical		[93]
CPT1	Etomoxir	Preclinical		[94–96]
	Perhexiline	Approved (Aust & NZ)		[97–99]

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Target	Agent	Phase of Development	Comments	Reference
	ST1326	Preclinical		[100, 101]
PLD	FIPI	Preclinical	Targets immune infiltration into tumors	[102]
	VU0155072–2	Preclinical	Targets immune infiltration into tumors	[102]
FABP	EI-05	Preclinical		[103]
	SBFI-102, 103	Preclinical		[104]
Choline kinase	HC-3, JCR and MN derivatives	Preclinical		[105]
	Triterpene quinone methides	Preclinical	Derived from natural products	[106]
	ICL-CCIC-0019	Preclinical		[107]
	EB-3D, EB-3P	Preclinical		[108–110]
Farnesyltransferase	tipifarnib	Phase I/II	Phase II studies in metastatic BC and squamous cell carcinoma; Phase I trial in glioblastoma	[111–113]
	lonafarnib	Phase I/Ib	Largely combination studies in glioblastoma, BC	[114–116]
	BMS-214662	Phase I	Single agent or in combination with paclitaxel in advanced solid tumors	[117, 118]
Palmitoylation	2-bromopalmitate	Preclinical		[119–121]
Acid sphingomyelinase	Fluphenazine	Preclinical		[122]