Greasing the Wheels of the Cancer Machine: The Role of Lipid Metabolism in Cancer

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Altered lipid metabolism is among the most prominent metabolic alterations in cancer. Enhanced synthesis or uptake of lipids contributes to rapid cancer cell growth and tumor formation. Lipids are a highly complex group of biomolecules that not only constitute the structural basis of biological membranes but also function as signaling molecules and an energy source. Here, we summarize recent evidence implicating altered lipid metabolism in different aspects of the cancer phenotype and discuss potential strategies by which targeting lipid metabolism could provide a therapeutic window for cancer treatment.

Among the biomolecules that make up cells, lipids often receive less attention than proteins and nucleic acids. However, lipids represent a complex group of biomolecules that vary in their structure and function, and their complexity is only fully appreciated as analytical methods to quantify these molecules are refined (Tumanov and Kamphorst, 2017). Lipids are hydrophobic molecules and include sterols, monoglycerides, diacylglycerides, triglycerides, phospholipids, and glycolipids. Many lipids are derived from fatty acids (FAs), a diverse group of molecules consisting of long hydrocarbon chains varying in length (number of carbon atoms) and saturation (number of double bonds). Mammals only produce certain FAs, i.e., those carrying double bonds up to the Δ9 position of the hydrocarbon chain. Other FAs, particularly polyunsaturated fatty acids (PUFAs), are essential and must be taken up (Nakamura and Nara, 2004). Unlike medium- and long-chain FAs, short-chain FAs (containing less than six carbon atoms) are mainly produced by commensal bacteria in the gut (Louis et al., 2014). Their roles in cellular processes, including epigenetic regulation, are outside the scope of this article as they have been extensively discussed elsewhere (Sabari et al., 2017).

When esterified to a glycerol moiety to form triglycerides, FAs provide an efficient energy storage that can be mobilized by fatty acid oxidation (FAO, also called β-oxidation) to generate ATP. FAs are also important components of membrane lipids, a group of amphipathic molecules that make up biological membranes. The most prominent type of membrane lipids are phospholipids, which can be subdivided into phosphoglycerides, in which two FAs are esterified to a glycerol backbone, and sphingolipids, in which one FA is linked to an amino alcohol (sphingosine). Phosphoglycerides also carry various head groups, including serine, ethanolamine, choline, glycerol, or inositol. Another type of membrane lipid are glycolipids, which are derived from sphingosine and FAs with a sugar head group (glucose or galactose) facing the outside of the membrane bilayer (Hishikawa et al., 2014). Glycolipids function in cell recognition, inflammation, and immune response (Jennemann and Gröne, 2013). The third major type of membrane lipid is cholesterol, consisting of four linked hydrocarbon rings, which not only controls membrane fluidity and microdomain formation (Lingwood and Simons, 2010) but is also a substrate for the synthesis of steroid hormones (Capper et al., 2016).

In addition to energy storage and membrane formation, FAs are also precursors for the synthesis of signaling molecules, termed lipid mediators. Arachidonic acid, an omega-6-derived PUFA, is the substrate for the synthesis of eicosanoids, including prostaglandins and thromboxanes, via the cyclooxygenase pathway (COX), and leukotrienes, via the lipo-oxygenase route. Prostaglandins, including prostaglandin E_2 (PGE_2), play a role in tissue inflammation and promote a pro-tumorigenic environment (Wang and Dubois, 2010). Other PUFAs with signaling function include the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which generally reduce inflammatory processes and are believed to lower the risk of breast and other cancers (Fabian et al., 2015).

Lipid mediators are derived from essential FAs, whose availability is largely determined by diet. However, they can also be obtained from membrane lipids by the action of phospholipases (Park et al., 2012). In particular, different isoforms of phospholipase A (PLA) release free FAs from phospholipids by cleaving the ester bond either at the sn-1 or sn-2 site (Figure 1). Due to the differential preference of saturated and unsaturated FAs located at these sites, different PLA isoforms selectively alter the availability of different free fatty acids (FFAs) (Park et al., 2012). The remaining lysophospholipid can be modified by lysophospholipase D to produce lysophosphatidic acid (LPA), which has multiple signaling functions (Mills and Moolenaar, 2003). LPA binds to a family of at least six different G protein-coupled receptors (GPCRs), triggering the activation of the RAS, PI3K, RAC, and RHO signaling axes to promote cell migration and survival (Moolenaar and Perrakis, 2011), with different receptors displaying preference for LPA molecules containing acyl chains of different lengths and degrees of saturation (Taniguchi et al., 2017). Interestingly, the lysophospholipase D autotaxin

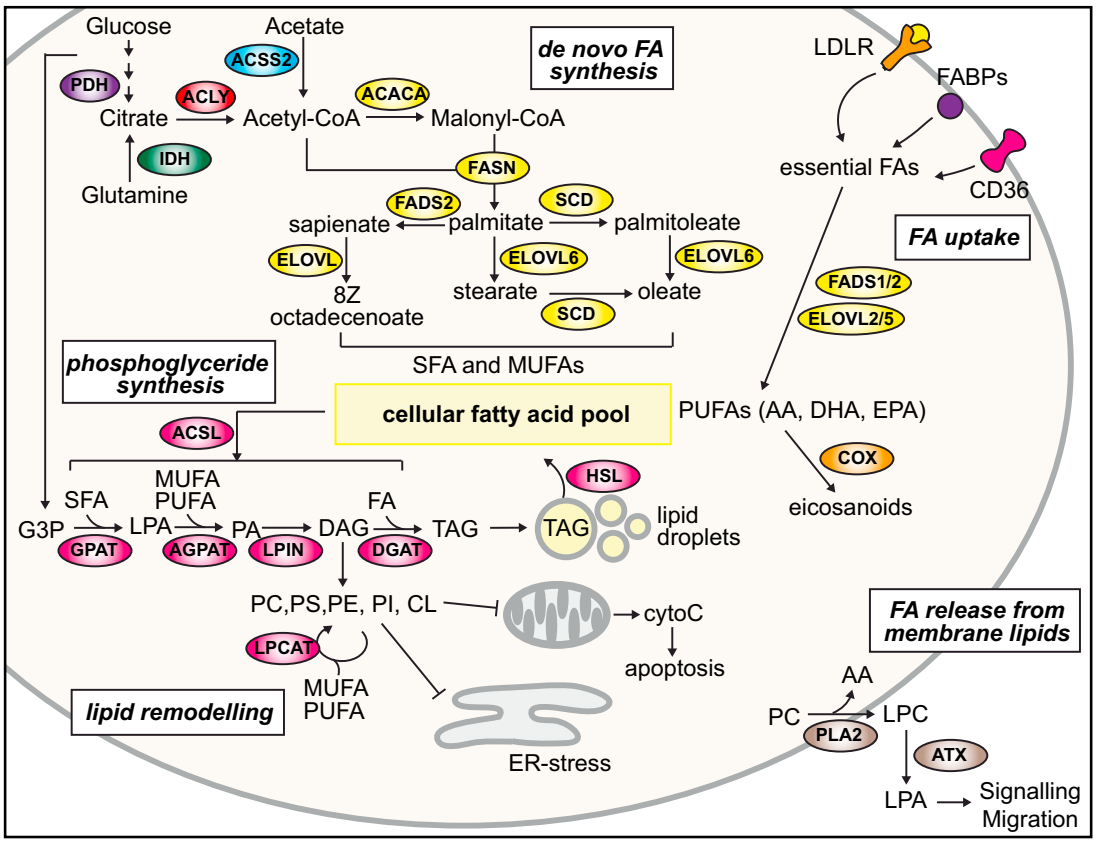

Figure 1. Lipid Provision in Cancer Cells

Fatty acid synthesis uses the substrate acetyl-CoA, which can be generated from glucose, glutamine, or acetate. The product of *de novo* fatty acid synthesis is palmitate, which is further elongated and desaturated to form saturated and monounsaturated fatty acids. Essential fatty acids are provided by lipid uptake and further modified by elongases and desaturases. Mobilization of free fatty acids from triacylglycerides also contributes to the cellular fatty acid pool. Fatty acids are used as substrates for phosphoglyceride synthesis and lipid remodeling via the Lands' cycle. Polyunsaturated fatty acids are also converted into eicosanoids, which have important signaling functions. The release of fatty acids from membrane lipids not only produces substrates for eicosanoid synthesis but also leads to the formation of the signaling molecule lysophosphatidic acid. The relative abundance of monounsaturated fatty acids in membrane lipids prevents the induction of ER stress, mitochondrial dysfunction, and the release of cytochrome *c* from the inner mitochondrial membrane.

PDH, pyruvate dehydrogenase; IDH, isocitrate dehydrogenase; ACLY, ATP-citrate lyase; ACSS2, acetyl-CoA synthetase; ACACA, acetyl-CoA carboxylase A; FASN, fatty acid synthase; SCD, stearoyl-CoA desaturase (Δ9); ELOVL, fatty acid elongase; ELOVL6, fatty acid elongase 6; LDLR, low-density lipoprotein receptor; FABP, fatty acid-binding protein; CD36, fatty acid translocase/scavenging receptor; FADS, fatty acid desaturase (Δ5 or Δ6); COX, cyclooxygenase/prostaglandin-endoperoxide synthase; GPAT, glycerol-3-phosphate acyltransferase; AGPAT, 1-acylglycerol-3-phosphate O-acyltransferase; LPIN, phosphatidate phosphatase LPIN1; DGAT, diacylglycerol O-acyltransferase; LPCAT, lysophosphatidylcholine acyltransferase; HSL, hormone-sensitive lipase; PLA2, phospholipase A2; ATX, autotaxin/ENPP2; FA, fatty acid; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; AA, arachidonic acid; DHA, docohexaenoic acid; EPA, eicosapentaenoic acid; G3P, glycerol-3-phosphate; LPA, lysophosphatidic acid; PA, phosphatidic acid; DAG, diacylglycerol; TAG, triacylglycerol; cytoC, cytochrome *c*; PC, phosphatidylcholine; PS, phosphatidylserine; PE, phosphatidylethanolamine; CL, cardiolipins; LPC, lysophosphatidylcholine; PI, phosphatidylinositol.

(ATX/ENPP2) has recently been shown to induce a stromal cancer signaling axis that promotes tumor progression in pancreatic cancer (Auciello et al., 2019).

These multiple roles of FAs in membrane structure, energy metabolism, and signaling highlight the importance of processes that control FA levels in cancer cells. This includes the regulation of FA synthesis, modification, and uptake from the microenvironment and their release from other lipid species. In the following sections, we will consider different mechanisms that control FA abundance in cancer cells.

Lipid Provision in Cancer

While most somatic cells obtain their lipids either from dietary sources or from lipids synthesized by the liver, various cancers reactivate *de novo* lipogenesis making them more independent from externally provided lipids.

Fatty Acid Synthesis, Modification, and Uptake

FAs are synthesized from cytoplasmic acetyl-CoA, which is generated from glucose, glutamine, or acetate (Pietrocola et al., 2015). Acetyl-CoA is then activated by acetyl-CoA carboxylases (ACC1/2, also known as ACACA/B) to form malonyl-CoA; subsequent condensation steps catalyzed by fatty acid synthase (FASN) then form the 16-carbon saturated FA palmitate. Palmitate is then elongated by fatty acid elongases (ELOVL1–7) and desaturated by stearoyl-CoA desaturases (SCD and SCD5 in humans) or fatty acid desaturases (FADS1–3) to form the cellular pool of non-essential FAs, including the 18-carbon monounsaturated FA oleate (C18:1) (Figure 1).

Increased FA synthesis in different cancers is well documented and multiple studies have shown that lipogenesis is essential for tumor growth (see Röhrig and Schulze, 2016 and references therein). Indeed, multiple oncogenic signaling pathways converge on FA synthesis. The PI3K/Akt signaling axis increases the expression of enzymes required for FA synthesis (discussed in more detail below) but also increases the phosphorylation and activation of ATP-citrate lyase (ACLY), the enzyme catalyzing the production of acetyl-CoA from cytoplasmic citrate (Bauer et al., 2005; Berwick et al., 2002). Conversely, the AMP-activated protein kinase (AMPK), controlled by the STK11/LKB1 tumor suppressor pathway, blocks FA synthesis by phosphorylating ACC (Shackelford and Shaw, 2009).

While early studies demonstrated *de novo* FA synthesis in cancer, they also concluded that cancer cells must also obtain at least some lipids from the extracellular milieu (Medes et al., 1953). Lipid uptake can be achieved through multiple routes, including the receptor-mediated endocytosis of low-density lipoprotein (LDL) particles via the LDL receptor (LDLR), as elucidated by the seminal work of Goldstein and Brown (Brown and Goldstein, 1986). Furthermore, FFAs are imported via the CD36 fatty acid translocase or the fatty acid transport proteins (FATPs of the SLC27 family of solute carriers) (Kazantzis and Stahl, 2012). FA uptake is also aided by fatty acid-binding proteins (FABPs), a family of proteins involved in FA uptake and transport (Furuhashi and Hotamisligil, 2008).

The increase in *de novo* FA synthesis in cancer cells alters cellular lipid composition and can be used for diagnostics (Hilvo et al., 2011). It also reduces the relative amount of PUFAs, which are obtained through uptake, but increases the amount of saturated and monounsaturated fatty acids (MUFAs) in membrane lipids. This protects from lipid peroxidation, caused by the peroxidation of PUFAs in the presence of reactive oxygen species (ROS) (Rysman et al., 2010). In this study, depletion or inhibition of FA synthesis using Soraphen A altered membrane dynamics and rendered cancer cells more susceptible to oxidative-stress-induced cell death (Rysman et al., 2010). However, FA uptake can also be essential for cancer as uptake of extracellular FAs, including palmitic acid, was shown to promote migration and metastasis in squamous cell carcinoma (Pascual et al., 2017). Similarly, inhibition of FA uptake via CD36 blockade has been shown to provide therapeutic benefit in preclinical models of prostate cancer (Watt et al., 2019). However, the relative contribution of *de novo* synthesis and uptake also depends on the availability of different lipid species within the extracellular milieu. While this can be influenced by the lipid composition of the diet, heterogeneity in the tumor microenvironment, for example, due to insufficient vascularization, also has a major effect on local lipid availability.

Cholesterol Biosynthesis

Cholesterol, an essential component of biological membranes, is generated from isoprenoid precursors produced by the mevalonate pathway. This pathway catalyzes the sequential condensation of two-carbon units from acetyl-CoA to form 3-hydroxy-3-methylglutaryl CoA, which is subsequently reduced to form mevalonate. Subsequent reactions form the isoprenoid farnesyl-pyrophosphate (FPP), which can be used for protein prenylation and ubiquinone (coenzyme Q10), hema A, or dolichol synthesis (Mullen et al., 2016).

Multiple studies have shown that inhibiting cholesterol synthesis is detrimental to cancer cells (see Mullen et al., 2016 and references therein). Indeed, its inhibition by statins, a class of compounds inhibiting HMG-CoA reductase, the rate-limiting enzyme of the pathway, has already been tested as an anti-cancer agent in clinical trials. While several studies reported beneficial effects of mevalonate pathway inhibitors in reducing cancer risk (Lee et al., 2009; Liu et al., 2016a; Sehdev et al., 2014), other studies failed to demonstrate a clear effect of statins in cancer prevention or as adjuvant therapy (Gray et al., 2017; Lim et al., 2015). However, it should be considered that most clinical trials used doses similar to those used for lipid-lowering treatment (e.g., 20–40 mg simvastatin per patient per day). Preclinical studies demonstrating clear anti-tumor efficacy in mouse models applied substantially higher doses (e.g., 60 mg simvastatin per kg per day; Li et al., 2017b), which are well tolerated. Clinical trials to evaluate high-dose statin treatment, either alone or as combination treatment, are still outstanding.

While the mevalonate pathway is clearly relevant for normal cellular function, the relative contribution of different metabolic outputs of the mevalonate pathway to cancer cell growth and survival is not fully understood. Inhibition of cholesterol production impairs the normal function of biological membranes, for example, by altering fluidity or preventing lipid raft formation (Sezgin et al., 2017). Furthermore, reducing the availability of the mevalonate pathway intermediate FPP blocks the prenylation of small G proteins, thus limiting cancer cell growth and migration (Freed-Pastor et al., 2012; Shamma et al., 2009). However, increasing evidence suggests that other products of the mevalonate pathway also play a role in cancer cells. One of these is ubiquinone, an essential electron transfer molecule within the respiratory chain. While many cancer cells downregulate mitochondrial metabolism (as part of the switch to aerobic glycolysis, also known as the Warburg effect), it is becoming increasingly clear that mitochondrial activity is still of importance in cancer cells. For example, it was shown that mitochondrial activity supports cancer cell survival under glucose limitation, which could be present in poorly vascularized tumors (Birsoy et al., 2014). Thus, impairing the respiratory chain by reducing ubiquinone availability could reduce cancer cell survival during nutrient restriction. Moreover, ubiquinone is important for the regulation of ROS formation by the respiratory chain (Wang and Hekimi, 2016), suggesting a close connection between the mevalonate pathway and redox control. Moreover, it was shown that ubiquinone provided by the mevalonate pathway supports pyrimidine biosynthesis and prevents oxidative stress in colorectal and pancreatic cancer (Kaymak et al., 2019; McGregor et al., 2019). A recent study showed that increased squalene production due to loss of squalene monooxygenase (squalene epoxidase, SQLE) in cholesterol auxotroph cells prevents oxidative cell death (Garcia-Bermudez et al., 2019). Together, these findings indicate that the mevalonate pathway has several essential outputs in addition to cholesterol, likely important for cancer cell survival (Figure 2A).

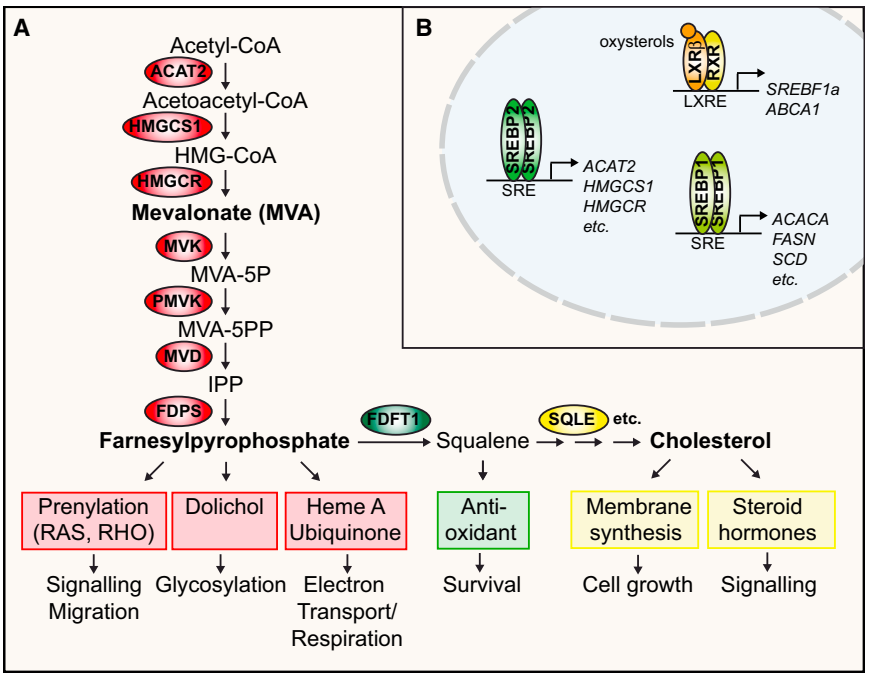

Figure 2. Metabolic Outputs of the Mevalonate Pathway

(A) The substrate of the mevalonate pathway is acetyl-CoA, which is sequentially condensed to form the 15-carbon isoprene farnesylpyrophosphate (FPP). FPP can be further converted to squalene and subsequently cholesterol, via the cholesterol biosynthesis pathway. Cholesterol is required for membrane synthesis and as a substrate for the synthesis of steroid hormones. FPP can also be used for the prenylation of small GTPases (RAS and RHO), the synthesis of dolichol or the production of the isoprene chains in heme A or ubiquinone. Squalene itself has an antioxidant function and contributes to cell survival. ACAT2, acetyl-CoA acetyltransferase 2; HMGCS, 3-hydroxy-3-methylglutaryl-CoA synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; MVK, mevalonate kinase; PMVK, phosphomevalonate kinase; MVD, mevalonate diphosphate decarboxylase; FDPS, farnesyl diphosphate synthase; FDFT1, farnesyl-diphosphate farnesyltransferase 1; SQLE, squalene epoxidase.

(B) Transcriptional regulators controlling expression of fatty acid and cholesterol biosynthesis genes are the sterol regulatory element-binding proteins (SREBP1 and SREBP2), which bind as homodimers to sterol regulatory elements (SREs) in the promoters of their target genes. The liver X receptor β (LXRβ, also known as nuclear receptor subfamily 1 group H member 2, NR1H2) binds as a heterodimer with the retinoid X receptor (RXR) to conserved LXR response elements (LXREs) in the promoters of the *SREBF1a* and *ABCA1* genes to promote lipid synthesis and cholesterol transport.

Cholesterol levels are also controlled both by the uptake of LDL particles and by cholesterol secretion via lipoproteins. For example, it was shown that LXR-623, a liver X receptor (LXR) agonist, reduces cancer cell viability and tumor growth in glioblastoma by inducing cholesterol efflux (Villa et al., 2016).

Transcriptional Regulation of Fatty Acid and Cholesterol Biosynthesis

Increased lipogenesis and mevalonate pathway activation are supported by enhanced expression of the enzymes belonging to these pathways, which are regulated by the sterol regulatory element-binding proteins (SREBPs) (Figure 2B). This family of helix-loop-helix leucine zipper (HLH-LZ) transcription factors consists of three isoforms: SREBP1a and SREBP1c encoded by the *SREBF1* gene, as well as SREBP2 encoded by the *SREBF2* gene (Bengoechea-Alonso and Ericsson, 2007). SREBPs are translated as inactive precursors residing as transmembrane proteins in the ER membrane where they are associated with a chaperone, the SREBP cleavage activating protein (SCAP). Depending on cellular sterol concentrations, SREBPs are either retained in the ER or transported to the Golgi, where a two-step proteolytic process releases the N-terminal half of the protein (Sakai et al., 1996; Wang et al., 1994). Mature SREBPs then translocate to the nucleus and bind as homodimers to the sterol regulatory elements (SREs) as well as E-boxes within the promoters of their target genes (Nohturfft and Zhang, 2009). While all SREBP isoforms can bind to SREs, they show some preference toward different promoters, with SREBP1 mainly regulating genes involved in FA synthesis, while genes of the cholesterol biosynthesis pathway are preferentially controlled by SREBP2 (Horton et al., 2003). Moreover, the different SREBP isoforms show tissue-specific expression, with SREBP1c being primarily in the liver (Nohturfft and Zhang, 2009) and SREBP2 in both liver and white adipose tissue (Madison, 2016). Interestingly, recent evidence from *Srebf2* knockout and hypomorphic mice demonstrated a role of SREBP2 in limb patterning during development and the ability of SREBP2 to induce expression of SREBP1a and SREBP1c (Vergnes et al., 2016).

Several studies have found that SREBPs are activated downstream of the oncogenic signaling pathways, primarily at the PI3K/Akt/mTORC1 signaling axis. Indeed, mTORC1 promotes mature SREBP1 nuclear accumulation, thus driving lipid synthesis during cell growth (Porstmann et al., 2008), and SREBP induction is a major transcriptional output of the mTORC1 pathway (Düvel et al., 2010). The mechanism underlying this regulation may involve phosphorylation and inactivation of the CREB-regulated transcription coactivator 2 (CRTC2) by mTORC1, leading to enhanced ER-Golgi transport of the SREBP/SCAP complex (Han et al., 2015). Moreover, mTORC1 regulates the subnuclear localization of mature SREBP1 by phosphorylation and cytoplasmic retention of phosphatidate phosphatase LPIN1, which in its unphosphorylated state inhibits SREBP1 by sequestering it in the nuclear periphery (Peterson et al., 2011). However, mTORC1-independent pathways controlling SREBP and hepatic lipogenesis downstream of Akt also exist (Yecies et al., 2011). Moreover, it was demonstrated that inhibiting oncogenic BRAF in melanoma blocks SREBP1 and that sustained lipid synthesis is associated with therapy resistance in this disease, further supporting the importance of lipid synthesis in cancer (Talebi et al., 2018). Regulation of lipid synthesis is also a key function of the transcription factor network associated with the Myc oncogene. MondoA (also known as MLXIP), a member of the Myc superfamily, was shown to be required for Myc-dependent tumorigenesis by regulating lipogenesis through SREBP1 (Carroll et al., 2015).

Moreover, it was shown that Myc cooperates with SREBP1 to drive lipogenesis during transformation in multiple cancer models (Gouw et al., 2019).

As mentioned above, SREBP processing is controlled by cellular sterol concentration, and variations in free cholesterol levels can alter SREBP activity. A recent study demonstrated that induction of the ATP-binding cassette transporter (ABCA1) by p53 increases the retrograde transport of cholesterol from the plasma membrane to the ER, thereby preventing SREBP2 maturation (Moon et al., 2019). However, the situation is further complicated by the fact that ABCA1 has originally been described to mediate cholesterol efflux (Quazi and Molday, 2011) and is itself controlled by the microRNA 33, encoded by an intron within the *SREBF2* gene (Gerin et al., 2010; Najafi-Shoushtari et al., 2010). Furthermore, regulation of cholesterol esterification and storage by the sterol O-acyltransferase 1 (SOAT1, also known as ACAT1) was shown to control SREBP activity and cancer cell survival in prostate cancer and glioblastoma (Geng et al., 2016; Yue et al., 2014).

The stability of mature SREBP is tightly controlled through ubiquitin-dependent regulation involving the F-Box and WD repeat domain containing protein 7 (FBXW7) (Sundqvist et al., 2005). Interestingly, all SREBP isoforms contain a conserved phosphodegron motif (CPD) that is recognized by the FBXW7/SCF complex (Welcker and Clurman, 2008). In SREBPs, phosphorylation of this motif by glycogen synthase kinase 3 (GSK3) induces ubiquitination and degradation (Sundqvist et al., 2005), and inhibition of GSK3 by AKT or the mTORC2 complex (Li et al., 2016) therefore results in the stabilization of mature SREBP. Furthermore, di-methylation of arginine 321 by protein arginine methyltransferase 5 (PRMT5) prevents SREBP1a phosphorylation by GSK-3beta and is found to be associated with poor prognosis in liver cancer (Liu et al., 2016b).

In addition to SREBPs, the liver X receptors, LXR-alpha and LXR-beta (Figure 2B), are likewise important drivers of lipogenesis in cancer (Lin and Gustafsson, 2015). These nuclear receptors form heterodimers with the retinoid X receptor (RXR) to induce gene expression in the presence of different oxysterols, which function as LXR ligands (Lin and Gustafsson, 2015). While LXRs are considered as targets for cancer therapy, the situation is complicated by findings showing that both LXR activation and inhibition are detrimental for cancer cell growth in different contexts. For example, as SREBP1c is among the LXR target genes, it was found that inhibiting LXR using the inverse agonist SR9243 blocked cancer cell growth by inhibiting glycolysis and lipogenesis. This resulted in reduced tumor growth across multiple systems (Flaveny et al., 2015), making LXR inhibition an attractive anti-tumor strategy. In contrast, as previously mentioned, LXR activation by different agonists has also been shown to reduce cancer cell survival, particularly in glioblastoma, by promoting cholesterol export (Guo et al., 2011; Villa et al., 2016).

The multiple mechanisms connecting lipogenic transcription factors to oncogenic signaling networks clearly demonstrate their importance for cancer cell growth and survival.

Driving the Cancer Phenotype

Lipids contribute to numerous processes that are deregulated in cancer. Multiple studies have addressed the effect of lipid biosynthesis inhibition on cancer cell survival and tumor growth (reviewed in Cheng et al., 2018 and Mullen et al., 2016). Compounds targeting FASN have been developed and tested in different cancer models (reviewed in Jones and Infante, 2015). Moreover, inhibition of ACC1 and ACC2 using the allosteric inhibitor ND-646 reduced tumor growth in both *Kras/p53*$^{-/-}$ and *Kras/Stk11*$^{-/-}$ mouse models of non-small-cell lung cancer either as single agent or in combination with carboplatin (Svensson et al., 2016).

In addition to their structural functions as components of cellular membranes, lipids also function as mediators of cancer-relevant phenotypes that promote transformation and tumor growth. For example, sphingolipids are major mediators of cellular signaling and survival (Ogretmen, 2018). However, in the following sections, we will mainly focus on the role of FAs in energy metabolism, stress response, and survival in cancer. We will also discuss recent evidence connecting lipid remodeling to ferroptosis, metastasis formation, stemness, and the heterotypic interactions within the tumor microenvironment.

Lipids in Energy Metabolism

Although reactivation of FA synthesis is now a well-established part of the metabolic reprogramming that takes place during transformation, it is becoming clear that FAO is likewise essential for cancer cell survival in various cancers. Overexpression of FAO enzymes has been noted in numerous malignancies (Ma et al., 2018) and blocking of FAO attenuates tumor growth in several tumor models. Inhibiting carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme in FAO, was shown to retard tumor growth and extend survival in an orthotopic-patient-derived xenograft (PDX) triple-negative breast cancer (TNBC) model (Camarda et al., 2016) and an orthotopic glioblastoma model (Lin et al., 2017). Enzymes upstream of CPT1 have also been identified as essential for tumor growth: acyl-CoA synthetase long chain 3 (ACSL3) converts FFAs into fatty acyl-CoAs, which can be used as substrate for lipid synthesis (Figure 1) or FAO. *Kras*^{G12D}-driven lung cancers overexpress ACSL3 and its ablation strongly reduces FA uptake, FAO, and tumor load (Padanad et al., 2016). Likewise, acyl-CoA-binding protein (ACBP) that binds to medium- and long-chain fatty acyl-CoA, likely functioning as a fatty acyl-CoA carrier or scaffold, is strongly upregulated in human glioblastoma, and its depletion inhibits FAO, leading to senescence in both an orthotopic xenograft and a genetic glioblastoma mouse model (Duman et al., 2019). In some cancers, FAO is activated by specific oncogenes, such as c-Myc in TNBC (Camarda et al., 2016) or mutant Kras in lung cancer (Padanad et al., 2016), in order to support proliferation. However, FAO is also essential for NADPH provision (Jeon et al., 2012; Lee et al., 2015; Pike et al., 2011; Wang et al., 2016), particularly during energetic stress such as glucose deprivation or anchorage-independent growth in which NADPH production by the pentose phosphate pathway (PPP) is impaired (Jeon et al., 2012). Mechanistically, this is dependent on AMPK, which phosphorylates and inactivates ACC, thereby blocking FA synthesis, which is a major consumer of cytosolic NADPH, but also activating FAO as malonyl-CoA; the product of ACC is an allosteric inhibitor of CPT1. Exactly how FAO-derived acetyl-CoA is used to generate cytosolic NADPH is not clear, but it is exported to the cytosol as citrate and then oxidized to α-ketoglutarate by isocitrate dehydrogenase 1 (IDH1) (Carracedo et al., 2013).

Stress Response and Cell Survival

Aside from being a source of ATP and NADPH, FAs are important structural components in the cell. One of the most abundant FAs in the cell is the MUFA oleic acid (C18:1). During *de novo* FA synthesis, SCD catalyzes the formation of a double bond at position Δ9 in stearic acid (C18:0) and, to a lesser extent, palmitic acid (C16:0) to form oleic and palmitoleic acid (C16:1), respectively (Figure 1). Numerous reports have demonstrated that inhibiting this reaction leads to ER stress and apoptosis in cancer cells cultured under lipid-depleted conditions *in vitro* (Ariyama et al., 2010; Griffiths et al., 2013; Williams et al., 2013; Young et al., 2013). In these systems, addition of exogenous oleic acid or other unsaturated FAs, such as the PUFAs linoleic (C18:2) or arachidonic acid (C20:4) (Ariyama et al., 2010), was sufficient to prevent ER stress and apoptosis induced by SCD inhibition (Griffiths et al., 2013; Williams et al., 2013; Young et al., 2013). Moreover, treatment with SCD inhibitors reduced tumor formation in xenograft models of gastric and colon cancer (Mason et al., 2012; Roongta et al., 2011), while SCD depletion blocked *in vivo* tumor growth of human lung cancer cells (Scaglia and Igal, 2008). Interestingly, SCD silencing also lowered the ability of human prostate cancer cells to form orthotopic xenograft tumors (Peck et al., 2016), indicating that exogenous lipids present in this organ cannot compensate for SCD function.

While these results demonstrate the importance of SCD for tumor growth, precisely how lack of desaturation leads to ER stress and apoptosis is not fully understood. It is well established that the accumulation of lipids containing saturated FAs leads to lipotoxicity and ER stress and lipids containing unsaturated FAs can reverse these effects (reviewed in Ackerman and Simon, 2014). Hence, it was proposed that altering the ratio of saturated and unsaturated FAs in the ER membrane toward increased saturation engages the unfolded protein response (UPR) (Ackerman and Simon, 2014). However, inhibiting desaturation also impairs mitochondrial respiration resulting in oxidative stress, suggesting ER stress induction could be indirect (Griffiths et al., 2013; Williams et al., 2013). Indeed, in addition to oleic acid, antioxidants can block the ER stress induction following SCD depletion (Griffiths et al., 2013; Williams et al., 2013). Moreover, it was shown in prostate cancer cells that SCD inhibition reduces MUFA incorporation into cardiolipins, a specific class of lipids only found in the inner mitochondrial membrane (Peck et al., 2016). A similar reduction in cardiolipin synthesis was demonstrated in response to betulinic acid, a plant-based compound shown to block cancer cell growth by inhibiting SCD (Potze et al., 2016). Cardiolipins bind to cytochrome *c* and prevent its release from the inner mitochondrial membrane, thus controlling the intrinsic apoptosis pathway (Schug et al., 2012). In both studies, SCD inhibition coincided with increased cytochrome *c* release, resulting in apoptosis (Peck et al., 2016; Potze et al., 2016).

In most of the studies mentioned above, SCD inhibition or depletion was only effective when cells were deprived of exogenous lipids (reviewed in Peck and Schulze, 2016). This suggests that in the presence of ample extracellular lipids, cancer cells satisfy their need for unsaturated FAs via uptake. Furthermore, SCD requires NADPH and oxygen in order to function, indicating that under hypoxia cancer cells are reliant on exogenous supply of unsaturated FA-containing lipids. Interestingly, SCD expression is induced by hypoxia (Li et al., 2006), potentially to compensate for reduced catalytic activity under this condition. Moreover, maintaining SCD expression for FA desaturation under conditions of oxygen and lipid deprivation is an essential function of SREBP1 in glioblastoma cells (Lewis et al., 2015). The ability of cancer cells to utilize exogenous lipids for the provision of unsaturated FAs appears to be dependent on the type of oncogene expressed, and not all lipids are exploited equally. Cancer cells driven by the AKT/mTOR pathway are reliant on *de novo* lipogenesis, as mTORC1 increases SREBP activity (Porstmann et al., 2008). Using isogenic cell line pairs, it was demonstrated that cells expressing H-Ras^{V12G} or K-Ras^{G12D} rely on lipid uptake compared to myrAKT-expressing cells for unsaturated FA provision (Kamphorst et al., 2013). Likewise, when subjected to SCD inhibition in lipid-containing medium, proliferation and viability of myrAKT cells were much more impaired than that of H-Ras^{V12G} cells. However, both cell lines were equally sensitive to SCD inhibition in lipid-depleted medium (Kamphorst et al., 2013). Importantly, lipidomic analysis of spent media revealed that lysophospholipids (i.e., phospholipids containing only one acyl chain) are taken up to a far greater extent compared to phospholipids. Furthermore, lysophospholipids containing mono- or polyunsaturated acyl chains were strongly preferred over saturated lysophospholipids (Kamphorst et al., 2013), indicating that cancer cells selectively deplete specific lysophospholipid species from their environment. However, the mechanism of this selective lipid uptake remains to be elucidated.

While these results demonstrate that increased uptake can compensate for reduced FA desaturation due to hypoxia or SCD inhibition, it is also clear that MUFA provision could be limited in the tumor microenvironment. Interestingly, recent work has demonstrated that clear cell renal cell carcinoma (ccRCC) cells amass MUFAs, particularly oleic acid, in the form of triglycerides when there is abundant supply of exogenous lipids and/or oxygen. These are stored within lipid droplets, a specified organelle for the storage of lipids (Olzmann and Carvalho, 2019). However, once extracellular lipids and oxygen become limiting, oleic acid is released and incorporated into phospholipids (Ackerman et al., 2018). This mechanism is dependent on the enzymes diglyceride acyltransferase 1 and 2 (DGAT1 and DGAT2), which condense fatty acyl-CoA with diglycerides, thereby forming triglycerides that are subsequently incorporated into lipid droplets. This study showed that culturing ccRCC cells in media containing oleic acid before switching to lipid-depleted media rendered these cells insensitive to SCD inhibition, an effect prevented by DGAT1/2 depletion (Ackerman et al., 2018). Similarly, DGAT1/2 depletion impaired tumor growth in a xenograft ccRCC model and analysis of triglyceride composition both *in vivo* and *in vitro* after DGAT1/2 depletion showed increased proportion of saturated FAs (Ackerman et al., 2018).

Despite the importance of SCD as a provider of MUFAs, subsets of cancer cells were shown to be largely insensitive to SCD inhibition even under lipid deprivation. It was recently demonstrated that these cells can satisfy their demand for unsaturated FAs when SCD is inhibited, by relying on a promiscuous enzymatic activity of the enzyme FA desaturase 2 (FADS2) (Vriens et al., 2019). FADS2 is usually required for the conversion of the essential PUFAs linoleic (ω-6) and α-linoleic (ω-3) into other

PUFAs including arachidonic acid (Zhang et al., 2016). However, FADS2 can also desaturate palmitate to generate the FA sapienate containing a double bond at position Δ6 as opposed to the Δ9 position in palmitoleic acid synthesized by SCD (Figure 1). Sapienate production has been suggested to primarily take place when levels of palmitate are high (Park et al., 2016), i.e., when SCD is inhibited or not expressed (as is in the human sebaceous gland). Under those conditions, palmitate competes with the natural substrates of FADS2, linoleic, and α-linolenic acid (Park et al., 2016). Cancer cells insensitive to SCD inhibition produce sapienate when SCD is blocked, and this was dependent on FADS2, as its depletion rendered these cells sensitive to SCD inhibition (Vriens et al., 2019). Likewise, ectopic expression of FADS2 in cells otherwise sensitive to SCD inhibition induced resistance to SCD inhibition (Vriens et al., 2019). Importantly, sapienate levels and FADS2 expression were elevated in human liver and lung cancers compared to healthy tissues, and combined inhibition of FADS2 and SCD led to reduced tumor growth in a mouse hepatocellular carcinoma model (Vriens et al., 2019), confirming that at least some cancers use this alternate pathway for FA desaturation.

In addition to FA synthesis and uptake, the relative abundance of saturated and unsaturated FAs in membrane phospholipids is also regulated by lysophospholipid acyltransferases (LPLATs). LPLATs along with phospholipase A2 (PLA2) remodel cellular phospholipids in a series of de-acylation and re-acylation steps, known as the Lands' cycle (Figure 1). In this process, PLA2 hydrolyzes acyl chains at the sn-2 position of glycerophospholipids, leaving a 1-acyl-lysophospholipid, which then can be re-acylated by LPLATs. As different LPLAT enzymes differ in their preference for FA substrates and lysophospholipid targets, this process thus generates diverse phospholipid species (reviewed in Wang and Tontonoz, 2019).

One LPLAT isoform, namely lysophosphatidylcholine acyltransferase 3 (LPCAT3, also called MBOAT5), was shown to be important for regulating the ratio between unsaturated and saturated FAs in phospholipids during ER stress caused by SCD inhibition. Depletion of SCD in cancer cells caused upregulation of LPCAT3, but not other LPCAT isoforms. Moreover, while LPCAT3 depletion by itself did not lead to ER stress, it exacerbated ER stress following SCD1 depletion or exposure to palmitic acid (Ariyama et al., 2010; Rong et al., 2013).

The primary substrates of LPCAT3 are PUFAs, and depletion of this enzyme reduces incorporation of PUFAs into phosphatidylcholine (PC), resulting in more saturated membrane lipids (Ariyama et al., 2010; Rong et al., 2013, 2017). However, LPCAT3 was also shown to incorporate oleic acid into PC (Ariyama et al., 2010). Interestingly, in hepatocytes, increased LPCAT3 expression downstream of LXR was found to be essential for SREBP1 maturation and nuclear translocation (Rong et al., 2017). LPCAT3 depletion reduced the proportion of PUFAs in PC (primarily arachidonic and linoleic acid) and strongly impaired SREBP1 maturation (Rong et al., 2017). Thus, it appears that SREBP1 processing is sensitive to the desaturation of membrane lipids, which could be indicative of nutritional status (Rong et al., 2017). While the exact mechanism by which PUFA-containing PC promotes SREBP1 maturation is not resolved, this process was found to be SCAP dependent, indicating that membrane lipid desaturation could regulate ER membrane dynamics to promote SCAP/SREBP interaction or ER to Golgi translocation of SREBP (Wang and Tontonoz, 2019).

Lipid Metabolism and Ferroptosis

While increasing incorporation of PUFAs into phospholipids via enzymes like LPCAT3 is essential to maintain membrane fluidity, this carries a risk as high amounts of PUFA-containing membrane lipids sensitize cancer cells to ferroptosis, a specific form of cell death. PUFAs are readily oxidized by hydroxyl and peroxyl radicals, generated by the labile iron pool (Fe^{2+}) via the Fenton reaction. The resulting lipid-peroxyl radicals subsequently oxidize neighboring PUFAs, leading to a chain reaction, which, if proceeds unhindered, culminates in cell death (Yang and Stockwell, 2016). Several FA and lipid metabolism enzymes whose activity determines the FA composition of membrane phospholipids were demonstrated to be functionally important for ferroptosis (Friedmann Angeli et al., 2019). In fact, LPCAT3 was identified in a screen aimed at finding genes required for ferroptosis (Dixon et al., 2015). The same screen also identified another LPLAT, 1-acylglycerol-3-phosphate O-acyltransferase 3 (AGPAT3, also called LPAAT3), which acylates LPA to form phosphatidic acid (PA) during *de novo* lipid synthesis (Figure 1; Dixon et al., 2015). Both enzymes prefer PUFAs as substrates (Wang and Tontonoz, 2019) and sensitize cancer cells to ferroptosis by increasing the proportion of PUFA-containing phospholipids (Dixon et al., 2015).

The enzymes ACSL3 and ACSL4 were also shown to regulate FA composition of phospholipids and ferroptosis sensitivity. They activate FAs for incorporation into lipids (Figure 1), with different ACSLs exhibiting distinct substrate preference (Klett et al., 2017). ACSL4 has a strong preference for PUFAs and its expression correlates with ferroptosis sensitivity following inhibition of glutathione peroxidase-4 (GPX4) in a panel of breast cancer cell lines (Doll et al., 2017). GPX4 is essential for the removal of lipid peroxides in membrane lipids and its inhibition or ablation induces ferroptosis (Friedmann Angeli et al., 2014; Yang et al., 2014). While $ACSL4^{-/-}$ cells are resistant to GPX4 inhibition, they can be re-sensitized when cultured in the presence of exogenous PUFA. This is most likely due to ACSL3, as only ACSL3 and ACSL4 efficiently utilize PUFAs as substrates (Doll et al., 2017).

Interestingly, exogenous MUFAs protect against ferroptosis by displacing PUFAs from membrane phospholipids. This is ACSL3 dependent, as its ablation abolished the ferroptosis-resistant state induced by MUFAs (Magtanong et al., 2019). This is likely because ACSL4 prefers PUFAs as substrates while ACSL3 can activate both types of FAs (Doll et al., 2017). Consequently, in the presence of ACSL3, the FA composition of cellular phospholipids reflects the MUFA/PUFA ratio available from both uptake and *de novo* synthesis. In the absence of ACSL3, this ratio is skewed toward PUFA, as ACSL4 becomes the main enzyme for FA activation. Surprisingly, while the ferroptosis protection mediated by exogenous MUFAs is ACSL3 dependent, the same is not true for lipotoxicity, as oleic acid prevents apoptosis caused by exogenous palmitic acid in the absence of ACLS3 (Magtanong et al., 2019). This indicates that while ACSL3 is required for replacing PUFAs with MUFAs, therefore reducing ferroptosis sensitivity, other enzymes can introduce MUFAs into phospholipids thereby reducing overall

saturation without affecting the amount PUFA-containing phospholipids.

Together, it can be concluded that FA desaturation is intricately linked to cellular stress response pathways and the control of programmed cell death. Thus, maintaining the correct FA desaturation state is vital for cancer cell survival.

Cancer Cell Dissemination and Metastasis Formation

Metastasis is a complex process involving the dissemination of cancer cells from primary tumors into the blood or lymphatic system, colonization of other organs, and secondary tumor expansion at distant sites. Although metastasis is the prime cause of cancer-related deaths, it is still incompletely understood (Lambert et al., 2017). However, recent findings obtained in various systems indicate a major role of lipid metabolism in metastasis.

For example, FASN inhibition was shown to prevent the induction of metastasis formation observed after anti-angiogenic therapy withdrawal (Sounni et al., 2014), but the mechanism determining this essentiality is not resolved. SREBP1 was also shown to drive a transcriptional program indicative of epithelial to mesenchymal transition (EMT) in breast cancer by recruiting a SNAIL/HDAC1/2 repressor complex to the E-cadherin promoter (Zhang et al., 2019). However, this function of SREBP1 is mediated by its direct binding to the E-cadherin promoter rather than by its regulation of FA synthesis (Zhang et al., 2019).

Evidence for a more direct involvement of FAs in metastasis formation was provided by a study demonstrating that aggressive cancer cell lines, i.e., those that show a higher capacity for migration and tumor growth, express high levels of the enzyme monoacylglycerol lipase (MAGL), which releases FFAs from monoacylglycerol during lipolysis (Nomura et al., 2010). Expression of MAGL induced a specific lipid signature, indicative of aggressive disease, and in its absence, tumor growth was rescued by a high-fat diet (HFD) (Nomura et al., 2010), indicating that exogenous FAs can promote disease progression. Similarly, the increased metastasis formation observed in PTEN$^{-/-}$ prostate cancer, caused by enhanced cholesteryl-esters formation by SOAT1, was linked to continued expression of LDLR and increased essential FA uptake (Yue et al., 2014). Elevated uptake of FFAs via the FA transporter CD36 was shown to promote EMT in hepatocellular carcinoma (Nath et al., 2015). However, this was primarily attributed to the uptake of palmitate and oleate rather than essential FAs (Nath et al., 2015). Similarly, metastasis-initiating cells (MICs) derived from squamous cell carcinoma, a highly aggressive form of oral cancer, express high levels of CD36 together with a lipid metabolism gene signature (Pascual et al., 2017). Inhibition or depletion of CD36 had minor effects on primary tumor growth but strongly diminished metastasis, suggesting that FA uptake and metabolism promote cancer cell dissemination. Interestingly, in this study, exposing mice to palmitic acid or placing them on HFD enhanced metastasis formation in a CD36-dependent manner. While the exact role of exogenous FAs was not fully resolved in this system, there is evidence that MICs use FAs to generate energy through FAO. Treatment of mice bearing orthotopic oral tumors with anti-CD36 neutralizing antibodies abolished metastasis formation, thus pointing toward a potential treatment strategy (Pascual et al., 2017). Similarly, activation of an SREBP-dependent lipogenic program was found to drive metastasis formation in PTEN and PML-deleted prostate cancer (Chen et al., 2018). Here, HFD was sufficient to drive metastasis formation in a non-metastatic prostate cancer model. Together, these studies suggest a link between dietary FA provision and cancer progression.

In addition to FAs, the mevalonate pathway has also been linked to loss of tissue architecture and cancer progression. Mutant p53, which is frequently found in aggressive cancers, was shown to bind SREBP2 and activate the expression of enzymes of this pathway in breast cancer cells (Freed-Pastor et al., 2012). Mevalonate pathway activation results in the formation of FPP, which is required for the prenylation of small G proteins, including Ras and RhoA. Thus, the activation of a metabolic pathway can drive a signaling program essential for migration and invasion of cancer cells (Freed-Pastor et al., 2012). This is particularly intriguing, as mevalonate pathway inhibitors, already used to treat hypercholesterolemia, are currently investigated as anti-cancer agents.

In addition to preclinical data supporting the role of lipids in metastasis formation, studies using primary patient material also indicate that metastasizing cancer cells display alterations in lipid metabolism. Dissemination of cancer cells into bloodstream from primary tumor sites known as circulating tumor cells (CTCs) is a property displayed by metastatic tumors (Nagrath et al., 2007). A study on prostate cancer patients using label-free coherent anti-stokes Raman scattering microscopy revealed high lipid uptake and increased intracellular lipid accumulation in CTCs (Mitra et al., 2012). A bioinformatic study focusing on The Cancer Genome Atlas (TCGA) pan-cancer data specifically aiming on patients with invasive tumors showed a higher frequency of amplification of genes associated with FA uptake and *de novo* lipid synthesis (Nath and Chan, 2016). Expression signatures for genes involved in FA synthesis, uptake, and metabolism were also correlated with an EMT score to identify common metastasis associated metabolic programs across different cancer types (Nath and Chan, 2016). While these studies highlight the importance of lipids in metastatic cancer patients, further investigation is required to delineate the exact contribution of FA synthesis and evaluate the exact role of lipid metabolism in metastatic cancer patients.

Lipid Metabolism in Cancer Stem-like Cells

Cancer stem-like cells (CSCs) or tumor-initiating cells (TICs) are considered to represent an important subpopulation differing from other cell populations within the heterogeneous tumor bulk. CSCs are characterized by a high potential for self-renewal, and they have been attributed to tumor initiation, treatment resistance, and relapse. Hence, therapeutic strategies specifically targeting CSCs have taken precedence. CSCs exhibit distinct metabolic features compared to non-CSCs, one of which is altered lipid metabolism, paving the way for the identification of unique vulnerabilities targeting this cell population (reviewed in Batlle and Clevers, 2017; Yi et al., 2018).

High levels of FASN expression and increased FA synthesis were linked to stem cell marker expression in glioblastoma (Yasumoto et al., 2016), and reduction of FASN activity was shown to mediate the inhibitory effect of resveratrol on CSC growth in breast cancer (Pandey et al., 2011). Interestingly, inhibitors of FA desaturation were identified in a screen for compounds selectively eliminating human pluripotent stem cells (Ben-David et al., 2013), and SCD inhibition was shown to induce ER stress,

increase sensitivity to temozolomide, and efficiently prevent tumor growth in glioblastoma CSCs (Pinkham et al., 2019). Moreover, a recent study found that a glioma stem cell-specific super enhancer drives ELOVL2 expression to promote the synthesis of PUFA-containing membrane lipids, increasing membrane fluidity and supporting epithelial growth factor receptor (EGFR) activity (Gimple et al., 2019). In ovarian cancer CSCs, an enhanced ratio of unsaturated to saturated FAs was identified using Raman spectroscopy. This was attributed to Δ9-desaturation, as SCD inhibition reduced the ability of ovarian cancer cells for sphere formation and to form tumors *in vivo* (Li et al., 2017a). Enhanced FA desaturation was also linked to the activation of a positive feedback loop involving NF-kB pathway, driving the expression of stem cell markers in ovarian cancer (Li et al., 2017a).

Another mechanism by which FA desaturation could contribute to stem cell function is the control of the Wnt/β-catenin signaling pathway. Activity of this pathway depends on the post-translational acylation of Wnt proteins by the porcupine O-acyltransferase (PORCN), which transfers acyl chains onto conserved cysteine and serine residues of the Wnt protein. Wnt acylation is important for its subcellular localization and its secretion into the extracellular space (Nusse, 2008). Using labeling and mass spectrometry, it was shown that the acyl group at serine 209 in Wnt-3a carries the MUFA palmitoleic acid (Takada et al., 2006). Indeed, PORCN was shown to prefer monounsaturated acyl-CoA as a substrate for Wnt acylation (Asciolla et al., 2017), and SCD activity is required for Wnt acylation and activation (Rios-Esteves and Resh, 2013). Interestingly, it was suggested that the bent conformation of MUFAs may assist their insertion into the hydrophobic grove of the frizzled receptor (Rios-Esteves and Resh, 2013). Thus, palmitoleate availability can determine Wnt pathway activity and regulate its downstream signaling via β-catenin stabilization. However, unsaturated FAs can also regulate β-catenin by a second mechanism involving the FAS associated factor 1 (FAF1), which binds to β-catenin accelerating its degradation (Kim et al., 2015). Unsaturated FA binding to FAF1 disrupts its association with β-catenin, leading to its stabilization and driving proliferation in ccRCC (Kim et al., 2015).

In addition to FAs, phospholipid remodeling also plays a role in CSC function, and ablation of LPCAT3 in intestinal stem cells (ISCs) leads to an increase in mature nuclear SREBP2 and increased expression of cholesterol biosynthetic enzymes, whereas expression of SREBP1 targets involved in FA synthesis is largely unaffected (Wang et al., 2018a). Interestingly, LPCAT3 ablation leads to ISC hyperproliferation, enhanced tumor formation, and reduced survival in APC^{min} mice (Wang et al., 2018a). This could be blocked by statins or pharmacological inhibition of lanosterol synthase (LSS) and was phenocopied by overexpression of mature SREBP2, indicating that enhanced cholesterol biosynthesis is responsible for enhanced intestinal tumor formation caused by LPCAT3 deletion (Wang et al., 2018a). Furthermore, induction of mevalonate pathway genes was shown to be involved in the induction of self-renewal and tumorigenicity of brain tumor-initiating cells by MYC (Wang et al., 2017a). Collectively, these findings indicate that FA and cholesterol synthesis are important drivers of the CSC phenotype.

Heterotypic Interactions in the Tumor Microenvironment

In addition to regulating cell intrinsic processes, lipids also participate in cell-cell communication and thus contribute to heterotypic interactions within the tumor microenvironment, which are important drivers of cancer development and progression. Heterotypic interactions involving lipids can range from signaling to attract or repel different stromal cell types to complex metabolic coupling circuits, providing cancer cells with additional fuel sources (reviewed in Baenke et al., 2013).

Production and release of signaling lipids or lipid mediators are tightly controlled and dependent on key lipid-modifying enzymes. Among these are the PLA2 isoforms, which cleave membrane phospholipids at the sn-2 position to release free PUFAs (Figure 1). Interestingly, some phospholipases are secreted proteins (Park et al., 2012), suggesting that cancer cells actively modify the tumor microenvironment lipidome. Lysophospholipids produced by these secreted phospholipases can be further converted to the signaling molecule LPA by extracellular ATX/ENPP2 (Federico et al., 2016), producing a chemotactic gradient that promotes dissemination of melanoma cells (Susanto et al., 2017). Similarly, it was recently shown that pancreatic stellate cells release lysophospholipids, which are converted to LPA by ATX/ENPP2 and promote progression in pancreatic cancer (Auciello et al., 2019).

While lipid-modifying enzymes, such as PLA2 and ATX/ENPP2, control the production of some lipid mediators, it is possible that altered FA synthesis and/or uptake in cancer cells favors the formation of specific classes of signaling lipids, for instance, by changing the availability of FAs of specific chain length and degree of saturation. For example, it was shown that cancer cells use exogenous palmitate not only to produce structural lipids but also to integrate this FA selectively into LPA molecules (Louie et al., 2013). As structural studies indicate that individual LPA receptors have differential preferences for LPA molecules carrying specific acyl chains (Taniguchi et al., 2017), altered FA synthesis and modification can also shape the lipid secretome of cancer cells to promote autocrine and paracrine signaling by lipid mediators.

During the degradation of phospholipids to lysophospholipids, cytoplasmic and secreted PLA2 isoforms release acylgroups that were previously bound to the sn-2 position, as FFAs (Figure 1). These are mainly PUFAs, such as arachidonic acid, and this enables the synthesis of eicosanoids, a large group of lipid mediators mostly involved in the regulation of inflammation (Wang and Dubois, 2010). One of these, PGE_2, is produced from arachidonic acid by cyclooxygenases (PTGS1/COX1 and PTGS2/COX2). When secreted, PGE_2 has multiple signaling functions promoting cancer cell proliferation, migration, and angiogenesis (Wang and Dubois, 2010). Interestingly, PGE_2 production by COX2 was recently shown to produce a tumor-promoting microenvironment by inducing the production of IL-6, CXCL1, and G-CSF by myeloid cells, while blocking type I interferon production, thereby preventing T cell-dependent tumor elimination (Zelenay et al., 2015).

As arachidonic acid is produced from exogenous linoleic acid by ELOVL2 and ELOVL5 and the Δ5 and Δ6 desaturase FADS1 and FADS2, increased expression of these enzymes should promote eicosanoid production in cancer cells. As mentioned

above, ELOVL2 was identified as a mediator of PUFA metabolism in glioblastoma (Gimple et al., 2019). Moreover, early studies indicated that FADS2 promotes eicosanoid synthesis in breast cancer (Pender-Cudlip et al., 2013). As previously mentioned, FADS2 can also produce the MUFA sapienate from palmitate. This alternative metabolic pathway ensures the production of MUFAs when SCD is inhibited (Vriens et al., 2019). However, this substrate switch, which is promoted by palmitate accumulation, also reduces γ-linolenic acid production and can impair the production of signaling lipids, including eicosanoids and DHA. Interestingly, FADS1 and FADS2 are SREBP target genes (Griffiths et al., 2013; Matsuzaka et al., 2002), suggesting that these transcription factors can also regulate the production of lipid mediators.

In addition to signaling lipids, products of the mevalonate pathway can also affect the interaction between cancer cells and immune cells. The oxysterol metabolite 27-hydroxycholesterol mediates the effect of HFD on metastasis formation in breast cancer by increasing the numbers of metastasis promoting immune cells while blocking cytotoxic T cells activity (Baek et al., 2017). Moreover, increased amounts of cholesterol in the tumor microenvironment was recently shown to induce exhaustion in CD8+ T cells (Ma et al., 2019). Thus, enhanced cholesterol production by cancer cells could contribute to a tumor microenvironment hostile to the immune system.

A well-established example of heterotypic interaction is the metabolic symbiosis of cancer cells and adipocytes found in several different cancer entities, including ovarian (Nieman et al., 2011), breast (Wang et al., 2017b, 2018b), and colorectal (Wen et al., 2017) cancer as well as in melanoma (Wen et al., 2017) and leukemia (Ye et al., 2016). In this context, the presence of cancer cells induces lipolysis and mobilization of FAs in adipocytes. This process appears to be dependent on FA-binding protein 4 (FABP4) expression in adipocytes as inhibition of FABP4 attenuates lipolysis and secretion of FAs (Nieman et al., 2011; Wen et al., 2017). Likewise, in an orthotopic transplantation model of metastatic ovarian cancer using either FABP4 wild-type or null mice, it was demonstrated that FABP4 expression in adipocytes is essential for metastasis to the omentum (an abdominal fat pad, which is the primary location of metastases in ovarian cancer) (Nieman et al., 2011). Coculture of cancer cells with adipocytes leads to AMPK activation and increased FAO in the cancer cells (Nieman et al., 2011; Wang et al., 2017b; Wen et al., 2017). Interestingly, there is evidence suggesting that this AMPK activation is mediated by FAs secreted by adipocytes in a manner dependent on Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK2) (Wen et al., 2017). In breast cancer stem cells (BCSCs), FAO and FA uptake is activated through a different mechanism involving leptin secreted by adipocytes, which activates the JAK/STAT3 signaling pathway that in turn activates FAO through STAT3 binding to the promoter of the *CPT1B* gene, a key regulator of FAO (Wang et al., 2018b). Interestingly, FAO of adipocyte-derived FAs is essential for stem cell maintenance in breast cancer, as FAO inhibition reduces proliferation and tumor-sphere formation in BCSCs, and activation of FAO was sufficient to restore tumor-sphere formation in STAT3-inhibited BCSCs (Wang et al., 2018b). Together with similar findings from leukemic stem cells (Ye et al., 2016), these studies demonstrate that adipocyte-derived FAs are an essential component of the cancer stem cell niche.

The Road Ahead

The numerous studies discussed here highlight the intricate relationship between oncogenic signaling and lipid metabolism regulation to promote cancer cell growth and survival, to regulate the processes that initiate cell dissemination and metastasis formation, and to control the communication between cancer and immune cells within the cancer microenvironment. They also underline the importance of the balance between the need for PUFAs for the production of lipid mediators that control immune evasion and their potentially damaging effect in sensitizing toward lipid peroxidation and ferroptosis.

Different strategies to target altered FA and cholesterol synthesis for cancer therapy have already been explored. Due to their widespread use, statins have been evaluated for their ability to reduce cancer risk and are currently tested in multiple clinical trials as anti-cancer agents (Mullen et al., 2016 and references therein). However, most compounds targeting FA metabolism have not progressed beyond preclinical studies (Röhrig and Schulze, 2016). A notable exception is the FASN inhibitor TVB-2640, which is currently evaluated in phase II clinical trials either as a single agent in *KRAS* mutant non-small-cell lung cancer (NCT03808558) or in combination with paclitaxel and trastuzumab in triple-negative breast cancer (NCT03179904). The ACC1/2 inhibitor ND-630, originally developed for the treatment of non-alcoholic steatohepatitis, is currently undergoing phase I testing (NCT02876796).

It is likely that simple treatment strategies inhibiting FA and cholesterol biosynthesis could be easily overcome by compensation through dietary lipids, but more specific approaches for intervention are needed. For example, selective targeting of FA desaturation in tumors with high rates of *de novo* FA synthesis not only prevents the formation of essential MUFAs but also causes the accumulation of saturated FAs, which are toxic to cells (Ackerman and Simon, 2014). As potent bioavailable SCD inhibitors, such as CVT-12 and 012, are becoming available (Koltun et al., 2009), it will be possible to evaluate their effect on tumor growth in immunocompetent animal models.

Successful treatment strategies may require a combination of inhibitors targeting both FA synthesis and uptake. Alternatively, anti-angiogenic therapies or specific dietary regimens could be used to starve tumors of exogenous lipids and prevent compensation. Indeed, the FASN inhibitor TVB-2640 is currently undergoing clinical testing in combination with the anti-angiogenic drug bevacizumab in high-grade astrocytoma (NCT03032484). Instead of blocking FA provision per se, it is also possible to target those enzymes that are required for the conversion of FAs into the different biomolecules essential for cancer growth. Blocking FA activation by targeting acyl-CoA synthetases or their ligation to the glycerol backbone by targeting acyltransferases would affect both endogenous and exogenous FAs, again overcoming the problem of compensation.

Other potential treatment strategies exploit the selective metabolic liabilities that are created by altered lipid metabolism in cancer. For example, enhanced lipid synthesis creates a high demand for reducing cofactors and increases the dependence of cancer cells on NADPH regenerating pathways.

Compounds that reduce the ability of cancer cells to produce NADPH by blocking the PPP or the activity of the malic enzymes would therefore be particularly toxic in tumors that show high rates of FA biosynthesis. Recently, polydatin, a selective inhibitor of glucose-6-phosphate dehydrogenase (G6PD), has shown anti-tumor activity in a preclinical model of metastatic tongue cancer by increasing oxidative stress (Mele et al., 2018). Similarly, excess lipid storage caused by the reduced ability to perform FAO in VHL-deficient ccRCC cells causes a selective sensitivity toward inhibition of the glutathione biosynthesis pathway, resulting in lipid peroxidation and induction of ferroptosis (Miess et al., 2018).

In addition to providing building blocks for essential cellular components, lipids regulate multiple signaling processes and participate in cell-cell communication. Thus, targeting lipid provision could directly interfere with the activity of drivers of the transformation process, that may otherwise be difficult to target. CGX1321, an inhibitor of the Wnt acyltransferase PORCN, is currently undergoing phase I clinical trial for gastrointestinal tumors (NCT02675946 and NCT03507998). As Wnt acylation requires the production of palmitoleate by SCD (Rios-Esteves and Resh, 2013), combining CGX1321 with effective inhibitors of FA desaturation could more effectively block Wnt activity, although this may also potentiate toxicities associated with Wnt pathway inhibition (Madan and Virshup, 2015). Finally, the involvement of lipids in the heterotypic interactions between different cell populations within a tumor highlights the need for studying the effect of interfering with the lipid metabolism network in suitable *in vivo* models as targeting lipid metabolism could promote the anti-tumor immune response, especially in combination with anti-checkpoint therapies. Rational strategies for cancer therapies can be developed as soon as suitable pharmacological agents targeting different steps in FA and lipid metabolism become available.

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