The multifaceted roles of fatty acid synthesis in cancer

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Abstract | Lipid metabolism, in particular the synthesis of fatty acids (FAs), is an essential cellular process that converts nutrients into metabolic intermediates for membrane biosynthesis, energy storage and the generation of signalling molecules. This Review explores how different aspects of FA synthesis promote tumorigenesis and tumour progression. FA synthesis has received substantial attention as a potential target for cancer therapy, but strategies to target this process have not yet translated into clinical practice. Furthermore, efforts to target this pathway must consider the influence of the tumour microenvironment.

Fatty acid synthase (FASN). Mammalian FASN is a multifunctional enzyme containing seven catalytic domains: malonyl/acetyltransferase, β-ketoacyl-synthase, dehydrase, enoyl-ACP-reductase, β-ketoacyl-reductase, thioesterase and acyl carrier protein.

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Lipids, including sterols, isoprenoids, acylglycerols and phospholipids, are hydrophobic biomolecules. They are components of biological membranes, are used in energy metabolism and storage, and have important roles as signalling molecules. Many lipids are synthesized from fatty acids (FAs), a diverse class of molecules consisting of hydrocarbon chains of different lengths and degrees of desaturation. FAs form the hydrophobic tails of phospholipids and glycolipids, which, together with cholesterol, represent major components of biological membranes. Membrane lipids also give rise to second messengers, such as diacylglycerol (DAG) and phosphatidylinositol-3,4,5-trisphosphate (PIP3; also known as PtdIns(3,4,5)P_3), which are formed in response to extracellular stimuli. FAs can also be assembled into triacylglycerides (TAGs), nonpolar lipids that are synthesized and stored during high nutrient availability and that release ample energy when broken down.

Warburg *et al.*[1] discovered in the 1920s that tumours have a high rate of glucose uptake and perform glucose fermentation independently of oxygen availability. Later, Medes *et al.*[2] established that tumours convert glucose or acetate into lipids at a rate similar to that observed in liver[2]. Although this study concluded that "this process is probably too slow to supply the lipid needs of a rapidly growing tumour, and the tumour must therefore obtain its lipids preformed by the host", another study found that tumour cells generate almost all their cellular FAs through *de novo* synthesis[3]. Several decades later, fatty acid synthase (FASN) was identified as the tumour antigen OA-519 in aggressive breast cancer[4]. Numerous studies have since confirmed the importance of FA biosynthesis for cancer cell growth and survival[5,6] (FIG. 1).

The modular nature of lipids, particularly those containing several FAs, determines the enormous structural complexity in this class of molecules[7]. Moreover, lipids are energy-rich compounds that can be degraded to provide ATP and contribute to cellular bioenergetics. The regulation of lipid synthesis, modification, uptake and degradation is therefore essential for the maintenance of cellular physiology, and perturbation of the processes controlling lipid provision can inhibit cell survival. It is therefore no surprise that lipid metabolism, in particular FA biosynthesis, is increasingly recognized as a potential therapeutic target in cancer.

This Review summarizes the evidence for alterations in FA metabolism in cancer. We discuss the regulation of lipid metabolism and the contribution of the tumour microenvironment to lipid provision. We also explore roles of FAs in tumorigenesis that go beyond their function as components of cellular membranes or substrates for energy production. Finally, we discuss different approaches that might be used to disrupt lipid provision for cancer therapy.

FA biosynthesis in cancer

In adult humans, *de novo* FA biosynthesis (FIG. 2) is restricted mainly to the liver, adipose tissue and lactating breast[8]. Expression of FASN is also found in proliferating fetal tissues[9], suggesting that reactivation of FA synthesis in cancer cells could represent a reversion to a less-differentiated embryonic state. Alternatively, increased FA biosynthesis could be a response to the high metabolic demand of cancer cells or an adaptation to reduced availability of serum-derived lipids in the tumour microenvironment. Recent evidence also suggests that genomic alterations, such as deletion of chromosome 8p in breast cancer, activate FA synthesis[10] and indicates that FA synthesis is crucial for cancer development and progression.

Major steps in FA biosynthesis. The metabolic intermediate that provides the substrate for FA synthesis is cytoplasmic acetyl-CoA, which is produced through different

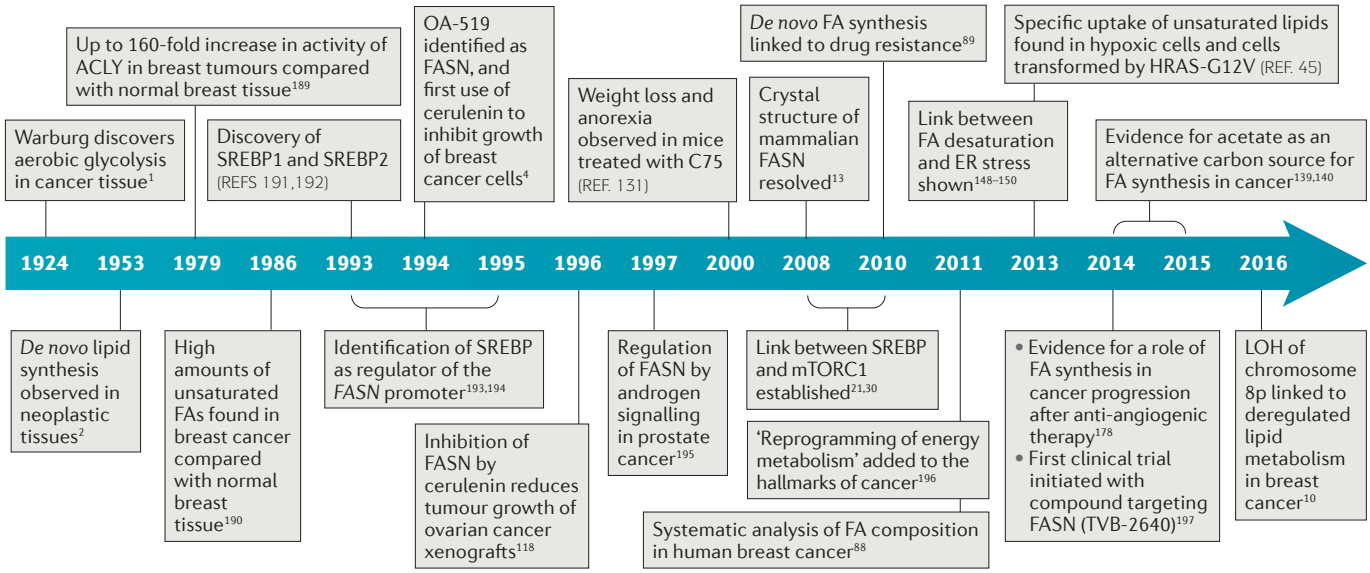


Figure 1 | **Fatty acid synthesis in cancer.** Major events demonstrating the importance of fatty acid (FA) synthesis in cancer cells. ACLY, ATP-citrate lyase; ER, endoplasmic reticulum; FASN, fatty acid synthase; LOH, loss of heterozygosity; mTORC1, mTOR complex 1; SREBP, sterol regulatory element binding protein.

mechanisms. Under normoxic conditions, normal cells use mainly pyruvate, the product of glycolysis, to feed the mitochondrial tricarboxylic acid (TCA) cycle[6]. This process generates citrate, which is cleaved into acetyl-CoA and oxaloacetate by ATP-citrate lyase (ACLY) in the cytoplasm[11]. Malonyl-CoA is then formed by acetyl-CoA carboxylases (ACCs, also known as ACACs), enzymes that are highly regulated by phosphorylation and allosteric regulation[12]. This regulation is important as malonyl-CoA determines the activity of carnitine palmitoyltransferases (CPTs), which couple acyl chains to carnitine for transport into the mitochondrial matrix and subsequent degradation by β-oxidation (BOX 1). The serial condensation of seven malonyl-CoA molecules and one priming acetyl-CoA by the multifunctional enzyme FASN[13] generates palmitate, the initial product of FA synthesis. This 16-carbon saturated FA (16:0) is then elongated and desaturated to produce molecules of various lengths and degrees of saturation[14,15]. Together with essential FAs taken up from the environment, they form a complex collection of substrates for the synthesis of FA-containing lipids.

Upstream regulators of FA biosynthesis

Expression of the enzymes involved in FA biosynthesis is controlled by sterol regulatory element binding proteins (SREBPs), a family of three basic-helix–loop–helix–leucine zipper (bHLH-LZ) transcription factors: SREBP1a and SREBP1c, two splice variants of the *SREBF1* gene, and SREBP2, the product of the *SREBF2* gene (REF. 16). SREBPs bind to sterol regulatory elements (SREs) and some E-box sequences in the promoters of their target genes[17]. These target genes also encode enzymes of the cholesterol biosynthesis pathway, discussed in greater detail by Mullen *et al.*[18] in this Focus, and the low-density lipoprotein receptor (LDLR), which is involved in receptor-mediated uptake of lipoprotein particles containing cholesterol and essential FAs.

FA synthesis requires large amounts of NADPH, an essential cofactor for biosynthetic reactions. SREBP also regulates several processes involved in the regeneration of NADPH, including enzymes of the oxidative pentose phosphate pathway, malic enzymes (ME1 and ME2) and isocitrate dehydrogenases (IDH1, IDH2 and IDH3)[19–21]. SREBP1 has also been connected to the one-carbon cycle[22], which provides methyl groups for the synthesis of phosphatidylcholine (PC) and other membrane lipids.

SREBPs are synthesized as inactive precursors that localize to the endoplasmic reticulum (ER) membrane[23]. Their activation requires proteolytic processing by Golgi-resident proteases (membrane-bound transcription factor site 1 protease (MBTPS1) and MBTPS2). The canonical pathways for the regulation of SREBP involve binding to the SREBP cleavage-activating protein (SCAP)[24]. This complex facilitates the translocation of SREBPs to the Golgi, where the SREBP amino termini are cleaved and released to enter the nucleus. Under conditions of high intracellular sterol, increased abundance of cholesterol in the ER membrane induces a conformational change in SCAP and causes it to bind to the products of the insulin-induced genes (INSIGs), leading to the retention of the SREBP–SCAP complex in the ER[25] (FIG. 3a). A second mechanism regulating SREBP processing is dependent on PC. Decreased PC levels in the Golgi membrane cause the translocation of MBTPSs from the Golgi to the ER membrane and specifically activate SREBP1 (REF. 22) (FIG. 3b). These modes of regulation establish an intricate feedback loop by coupling SREBP activation directly to the lipid content of intracellular membranes.

Although the early investigations into SREBP function concentrated on its role in controlling hepatic metabolism[26], it is now clear that these factors control transcriptional programmes that are highly relevant to cancer. First, it was shown that nuclear accumulation of

mature SREBP is induced in response to activation of AKT[27–29]. Induction of SREBP1 by AKT required the activity of mTOR complex 1 (mTORC1), suggesting that protein biosynthesis and lipid biosynthesis are regulated in a concerted manner during the induction of cell growth by the AKT–mTORC1 signalling axis[30]. SREBP target genes were also found to be a major component of the transcriptional response to mTORC1 activation[21], thus firmly establishing the link between oncogenic signalling and lipid metabolism. Interestingly, at least two mechanisms for the regulation of SREBP downstream of mTORC1 have been proposed. One of these involves the phosphatidate phosphatase lipin 1 (LPIN1), which converts phosphatidic acid into DAG, a precursor for the synthesis of phospholipids and TAGs. However, LPIN1 also has non-enzymatic roles as it can enter the nucleus and co-activate transcription of peroxisome proliferator-activated receptor-γ co-activator 1α

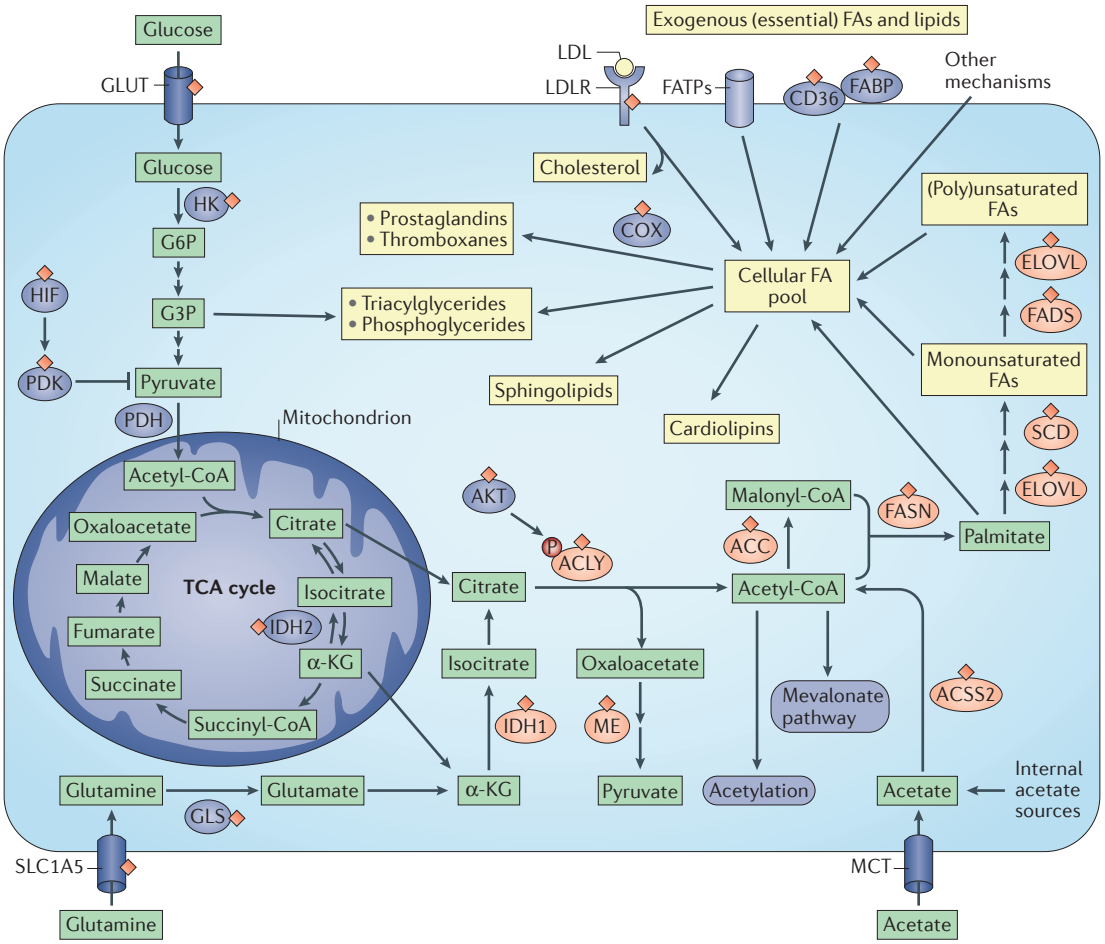


Figure 2 | **Fatty acid synthesis and uptake.** Overview of the metabolic pathways required for the *de novo* synthesis of fatty acids (FAs). Glucose or glutamine generates citrate, which is cleaved by ATP-citrate lyase (ACLY) to acetyl-CoA and oxaloacetate. ACLY is phosphorylated and activated by AKT. Acetyl-CoA can also be synthesized from acetate, which is taken up from the environment or provided by intracellular sources. Acetyl-CoA is then carboxylated to malonyl-CoA and condensed by FA synthase (FASN) in a repeat reaction to generate palmitate. Palmitate is then elongated by FA elongases (ELOVLs) and desaturated at the Δ9 position by stearoyl-CoA desaturases (SCDs). Other FA desaturases (FADSs) can introduce double bonds at the Δ5 or Δ6 position, or at Δ9 in long-chain FAs. Essential FAs (containing double bonds in positions higher than 9) have to be taken up from the bloodstream via the low-density lipoprotein (LDL) receptor (LDLR), FA transport proteins (FATPs) or FA translocase (FAT) together with FA binding proteins (FABPs). Short-chain FAs can also passively enter cells. Together, FAs generated through *de novo* synthesis and through exogenous uptake make up the pool of intracellular FAs that can be used for the synthesis of triacylglycerides for energy storage, glycerophospholipids, cardiolipins and sphingolipids for membrane synthesis, and eicosanoids for signalling processes. Enzymes known to be regulated by sterol regulatory element binding proteins (SREBPs) are shown in red. Proteins upregulated or activated in cancer are marked by red diamonds. α-KG, α-ketoglutarate; ACC, acetyl-CoA carboxylases; ACSS2, cytoplasmic acetyl-CoA synthetase; COX, cyclooxygenase; GLS, glutaminase; GLUT, glucose transporter; G3P, glyceraldehyde-3-phosphate; G6P, glucose-6-phosphate; HIF, hypoxia-inducible factor; HK, hexokinase; IDH, isocitrate dehydrogenase; MCT, monocarboxylate transporter; ME, malic enzyme; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase (acetyl-transferring) kinase; SLC1A5, solute carrier family 1 member 5; TCA, tricarboxylic acid.

β-Oxidation
The process by which fatty acids are sequentially degraded to acetyl-CoA, which can subsequently be oxidized by the mitochondrial tricarboxylic acid cycle to produce ATP.

E-Box sequences
Palindromic DNA element with the consensus sequence CANNTG, which is found in the promoters of many genes and mediates transcription factor binding.

Box 1 | **β-Oxidation**

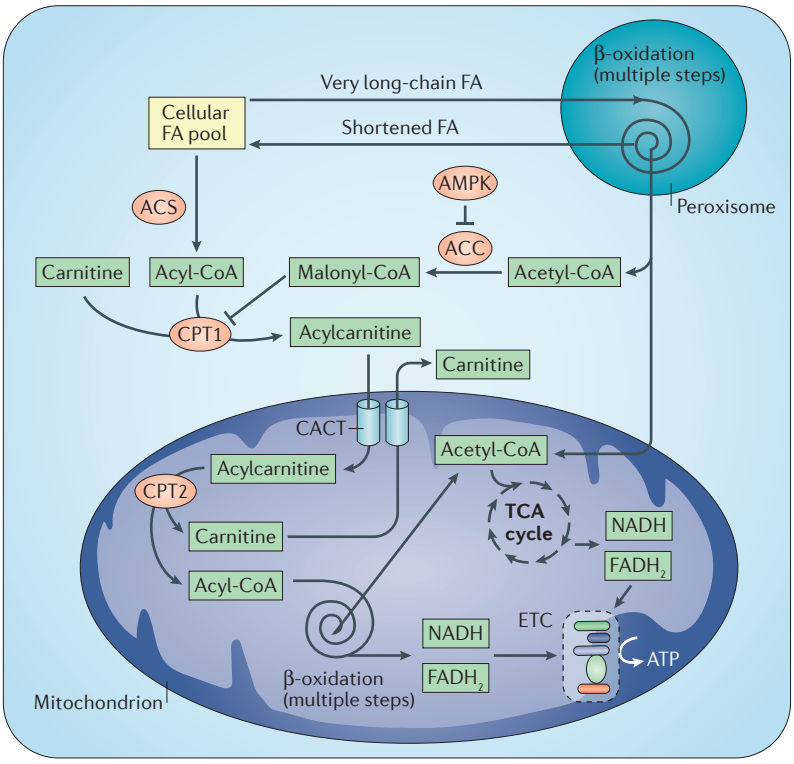
Fatty acids (FAs) are energy-rich compounds and their oxidation produces about twice the energy compared with carbohydrates (39 KJ g^{-1} for palmitate compared with 15 KJ g^{-1} for glucose (PubChem Compound Database)). FAs are also the preferred substrates for energy storage, mainly in the form of triacylglycerides (TAGs), which are stored in large vacuoles in adipocytes but are also found in smaller lipid droplets in many other cell types[182].

Generating energy from stored TAGs requires initial cleavage of acyl chains from the glycerol backbone through a process called lipolysis[183]. The resulting free FAs can be imported into mitochondria for degradation (see the figure). This requires their activation by coupling to CoA, followed by transfer of the acyl group to carnitine palmitoyltransferase 1 (CPT1). Acylcarnitine is then shuttled to the mitochondrial matrix by the carnitine–acylcarnitine translocase (SLC25A20, also known as CACT) and the acyl chain is transferred back to CoA by CPT2. Very long FAs require initial shortening in the peroxisomes[184].

β-Oxidation generates energy at several steps: the step-wise shortening of acyl-CoA generates one molecule of $FADH_2$ and NADH for every 2-carbon unit released. Each acetyl-CoA molecule then yields 3 molecules of NADH, 1 molecule of $FADH_2$ and 1 GTP in the tricarboxylic acid (TCA) cycle, resulting in a total yield of approximately 130 molecules of ATP for the degradation of the 16-carbon FA palmitate.

FA synthesis and degradation are mutually exclusive and regulated by negative feedback. The activity of CPT1 is blocked by high levels of malonyl-CoA, generated during the committed step of FA synthesis. Inhibition of acetyl-CoA carboxylases (ACCs) by AMP-activated protein kinase (AMPK)[185] reduces malonyl-CoA levels and enables the activation of β-oxidation for energy production.

Although the importance of lipid synthesis for the proliferation and survival of cancer cells is well established, much less is known about the role of β-oxidation in cancer. However, several reports have demonstrated that cancer cells require β-oxidation, particularly under stress conditions (reviewed in REF. 186). For example, the brain-specific CPT1C is induced by AMPK in response to metabolic stress in cancer cells to support energy generation when glycolysis is inhibited by rapamycin treatment[187]. More recently, it was shown that β-oxidation is an important bioenergetics pathway in triple-negative breast cancer and is required for the activation of SRC[188]. Targeting this pathway may limit the metabolic flexibility of cancer cells and should be considered as a strategy for cancer treatment.



ACS, acyl-CoA synthetase; ETC, electron transport chain.

(*PPARGC1A*; also known as *PGC1A*)[31]. LPIN1 also binds to mature SREBPs, resulting in their sequestration to the nuclear lamina, thus preventing their access to active promoters[32] (FIG. 3c). Phosphorylation by mTORC1 prevents nuclear translocation of LPIN1 and restores SREBP activity[32]. A second mechanism was discovered in hepatocytes, in which mTORC1 induces ER–Golgi translocation of SREBP1 by phosphorylating the CREB regulated transcription co-activator 2 (CRTC2), which usually functions as part of the transcriptional response to cyclic AMP (cAMP). CRTC2 normally inhibits SEC31A, a component of coat protein complex II (COPII) involved in vesicle budding[33]. Phosphorylation of CRTC2 by mTORC1 releases SEC31A from this inhibition and restores SREBP–SCAP translocation and SREBP processing (FIG. 3d).

Another layer of complexity in the regulation of SREBP activity is added by the finding that the stability of the mature form is controlled by F-box and WD repeat domain protein 7 (FBXW7), the substrate recognition subunit of the SCF^{FBXW7} E3–ubiquitin ligase complex, which is frequently mutated or deleted in human cancer[34]. FBXW7 binding to SREBP requires phosphorylation of SREBP by glycogen synthase kinase 3β (GSK3β)[35,36]. As GSK3β is inhibited through AKT-dependent phosphorylation, activation of AKT not only induces SREBP processing but also increases the stability of the mature form to drive the expression of lipid biosynthesis enzymes (FIG. 3c). So far, it is unclear whether these different mechanisms of SREBP regulation can function simultaneously, or whether they are dependent on cellular context or specific upstream signals. Nevertheless, the multifaceted interactions between SREBP and components of the AKT signalling pathway highlight the importance of this transcription factor in the regulation of macromolecule biosynthesis downstream of nutrient and growth factor sensing.

In addition to SREBPs, other nutrient-sensing transcription factors also contribute to the regulation of FA biosynthesis. Among these are the transcriptional activator MondoA (also known as MLXIP) and carbohydrate-responsive element-binding protein (ChREBP; also known as MLXIPL)[37]. It has been shown that ChREBP is activated in cancer cells in response to mitogenic signals to promote anabolic metabolism, including enhanced lipid biosynthesis[38]. Moreover, MondoA is induced by the proto-oncogene MYC to drive glutaminolysis and lipogenesis in cancer cells[39]. Interestingly, the synthetic lethality of blocking MondoA in cancer cells with high levels of MYC activity could be fully prevented by supplementation with monounsaturated FAs[39], confirming that these FAs are essential for cell proliferation and survival. Together, these results illustrate how multiple oncogenic pathways can converge on lipid synthesis to facilitate growth and proliferation of cancer cells.

Role of the tumour microenvironment

Although there is substantial evidence that tumours perform *de novo* FA synthesis, it is less clear whether this phenotype is driven solely by cancer cell-intrinsic

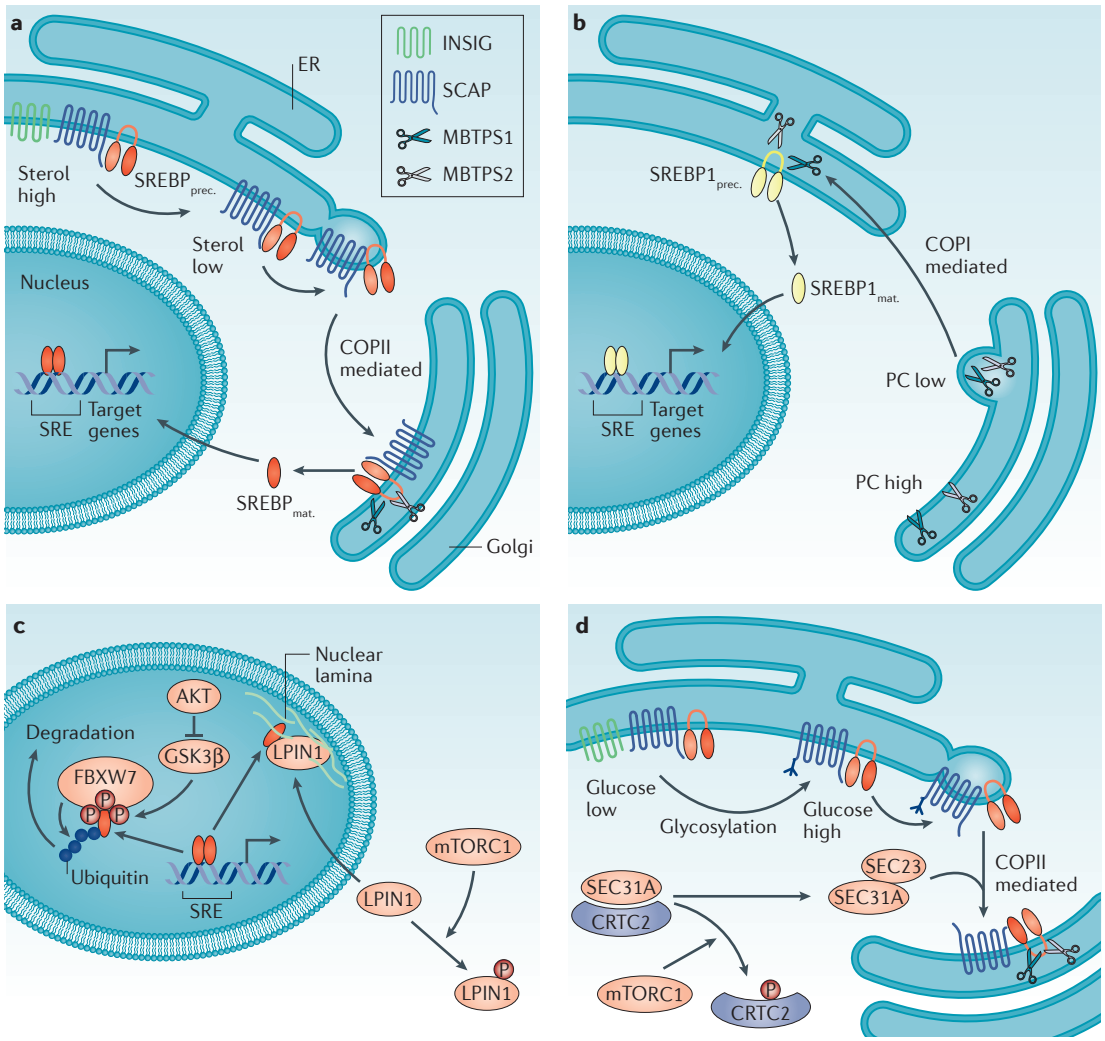


Figure 3 | **Regulation of SREBP activity on multiple levels. a** | Regulation of sterol regulatory element binding proteins (SREBPs) by regulated intramembrane processing. SREBPs (SREBP1a, SREBP1c and SREBP2) are translated as precursors ($SREBP_{prec.}$) in the endoplasmic reticulum (ER) membrane, where they bind to the SREBP cleavage-activating protein (SCAP). At low intracellular sterol levels, the SREBP–SCAP complex translocates to the Golgi via COPII-mediated transport. In the Golgi, membrane-bound transcription factor site 1 protease (MBTPS1) and MBTPS2, cleave off the amino terminus of SREBP ($SREBP_{mat.}$), which enters the nucleus and binds to sterol response elements (SREs) in promoters of target genes. When sterols are abundant, SCAP binds to the insulin-induced genes (INSIGs) and retains SREBP in the ER. **b** | SREBP1 can also be activated by low phosphatidylcholine (PC) levels through the translocation of MBTPS1 and MBTPS2 from the Golgi to the ER membrane via COPI-mediated transport. **c** | Regulation of nuclear SREBP. Phosphorylation of lipin 1 (LPIN1) by mTOR complex 1 (mTORC1) retains the protein in the cytoplasm and prevents it from sequestering SREBP to the nuclear lamina. The stability of nuclear SREBP is controlled by F-box and WD repeat domain protein 7 (FBXW7), which binds to a CDC4 phosphodegron motif on SREBP in response to phosphorylation by glycogen synthase kinase 3β (GSK3β), a negative target of AKT. **d** | Additional mechanisms of SREBP activation. Regulation of SREBP by mTORC1 through the phosphorylation of CREB-regulated transcription co-activator 2 (CRTC2), a negative regulator of COPII-dependent vesicle transport. Increased *N*-glycosylation of SCAP in response to AKT-induced glucose uptake results in the release of the SREBP–SCAP complex from inhibition by INSIGs.

processes or whether it is also modulated by environmental conditions. Many studies investigating FA synthesis in cancer cells use lipid-reduced culture conditions to limit access to exogenous lipids (for example, see REF. 40). Furthermore, addition of palmitate or oleate fully restores cancer cell viability after inhibition of FASN[4]. Thus, cancer cells should be able to use exogenous lipids when precursors are limited or FA synthesis is blocked.

Hypoxia

The tumour microenvironment is frequently hypoxic. Under hypoxia, entry of glucose-derived pyruvate into the TCA cycle is inhibited[41]. Cells must therefore switch to alternative carbon sources to generate acetyl-CoA for FA synthesis. These sources include the synthesis of citrate from glutamate via reductive carboxylation[42,43], and the direct synthesis of acetyl-CoA from acetate by cytoplasmic acetyl-CoA synthetase (ACSS2)[44].

Lipid droplets
Specialized organelles rich in neutral lipids, cholesterol and cholesteryl esters.

Lipid rafts
Highly specialized microdomains in the plasma membrane characterized by distinct lipid composition that act as platforms for the assembly of signalling molecules.

Raman spectroscopy
A label-free spectroscopic imaging technique that can be applied to tissue sections. It is based on a characteristic shift in the frequency of light used to illuminate a specimen.

Cachexia
Wasting syndrome characterized by atrophy of muscle and adipose tissue and extreme weight loss.

FA uptake. It is possible that the reduced FA synthesis in hypoxia is compensated by increased uptake of exogenous lipids. For example, an analysis of FA import in hypoxic cancer cells demonstrated that hypoxia increases lipid uptake, particularly of species containing monounsaturated acyl chains[45]. Another study found that hypoxia increases lipid uptake in breast cancer and glioblastoma cells by inducing the expression of FA binding protein 3 (FABP3) and FABP7 (REF. 46), which are involved in the uptake and subcellular trafficking of FAs. Hypoxia also promoted the storage of lipids in lipid droplets through induction of perilipin 2 (PLIN2)[46]. Upon re-oxygenation, cells used these stored lipids for energy production and antioxidant defence[46]. This increased the ability of the cells to survive the surge in oxidative stress associated with a sudden increase in oxygen availability. The flexibility to switch between FA synthesis, lipid uptake and degradation could be particularly important for cancer cells exposed to the temporal fluctuations in oxygen availability found in tumours[47,48].

Increased lipid uptake was also observed in cells transformed by oncogenic HRAS (HRAS-G12V), whereas cells transformed by constitutively active AKT (myristoylated AKT) showed increased *de novo* synthesis[45]. These results demonstrate that both genetic background and environmental conditions determine the relative dependence of cancer cells on this biosynthetic process, which has important therapeutic implications, as compensatory lipid uptake is likely to lead to resistance to inhibitors of FA synthesis. However, as poor perfusion will also reduce the availability of serum-derived lipids, tumour cells may be exposed to lipid gradients, similar to those described for glucose and oxygen[49] (FIG. 4). Differences in the relative abundance of substrates for FA synthesis will require some levels of adaptation, for example, through alternative pathways for the provision of acetyl-CoA (FIG. 4b). However, severe shortage of certain nutrients or prolonged lipid deprivation may render cancer cells highly dependent on one specific metabolic process. For example, as hypoxia prevents the use of glucose for FA synthesis, hypoxic cancer cells may become more dependent on lipid uptake (FIG. 4c). However, if exogenous lipids are also in short supply, cells may switch back to *de novo* FA synthesis but now fully depend on glutamine or acetate as alternative substrates (FIG. 4d). Consequently, inhibition of *de novo* FA biosynthesis may be most effective under conditions that limit metabolic flexibility. Alternatively, it may be required to target several routes of lipid provision simultaneously.

Although cancer cells activate *de novo* FA synthesis, they also require the uptake of essential FAs. For example, α-linolenic acid and linoleic acid carry double bonds beyond position 9 of the acyl chain; these cannot be synthesized by humans and have to be provided by diet. Essential FAs are important for multiple cellular functions, including the synthesis of signalling lipids and phosphoglyceride species found in lipid rafts. Evidence for the importance of essential FAs for tumour growth comes from a recent study that investigated lipid composition of prostate tumours using Raman spectroscopy[50]. This study found that aggressive prostate cancers show high amounts of lipid droplets containing cholesteryl esters (CEs). This was due to increased expression of sterol *O*-acyltransferase 1 (SOAT1, also known as ACAT1), which catalyses the conversion of free cholesterol into CE and its subsequent storage in lipid droplets. Through this mechanism, cancer cells prevent the accumulation of free cholesterol, which would normally block expression of the LDLR through sterol-dependent inhibition of SREBP. Maintaining LDLR expression supports proliferation by facilitating the uptake of essential FAs[50]. However, it is not clear whether uptake of essential FAs is influenced by hypoxia or how their provision can be maintained in poorly vascularized tumours.

Lipid modification. Hypoxia can also affect the ability of cancer cells to modify cellular lipids by regulating the activity of enzymes involved in FA desaturation. Moreover, hypoxia induces the formation of reactive oxygen species (ROS) responsible for lipid peroxidation (discussed below). Of particular interest in this context is the role of stearoyl-CoA desaturase (SCD), which catalyses the formation of double bonds at the Δ9 position of palmitoyl-CoA and stearoyl-CoA to generate monounsaturated FAs. As this reaction requires O_2, the synthesis of monounsaturated FAs is compromised under severe hypoxia[45]. However, expression of SCD was induced in response to intermittent hypoxia in mice[51] and after exposure to lipid- and oxygen-deprived conditions in glioblastoma cells[52], suggesting that reduced availability of oxygen for FA desaturation could at least partially be compensated by increasing SCD levels. In addition, roles for the Δ5 FA desaturase FADS1 and the Δ6 FA desaturase FADS2 are also emerging[53]. These enzymes are involved in the generation of polyunsaturated FAs (PUFAs), which are important modulators of inflammation and immune responses[54].

Metabolic symbiosis

It is well established that systemic mobilization of lipids from adipose tissue fuels tumour growth during cancer cachexia[55]. However, the immediate metabolic environment within a tumour is also constantly modified by the metabolic activity of both cancer and stromal cells. One consequence of this is the development of symbiotic relationships between different populations of cancer cells or between cancer and stromal cells. For example, cancer cells in well-oxygenized tumour areas use lactate produced by hypoxic cancer cells to fuel their oxidative metabolism[56]. Metabolite transfer has also been observed between cancer cells and cancer-associated fibroblasts (CAFs) (REF. 57 and references therein). Interestingly, lipids can also participate in metabolic symbiosis. Ovarian tumours preferentially metastasize to the omental adipose tissue where they induce the breakdown of TAGs and release of free FAs from adipocytes. Cancer cells take up these FAs for ATP production via β-oxidation[58] (BOX 1). Moreover, leukaemia stem cells evade chemotherapy by migrating to gonadal fat tissue, where they use adipose-derived

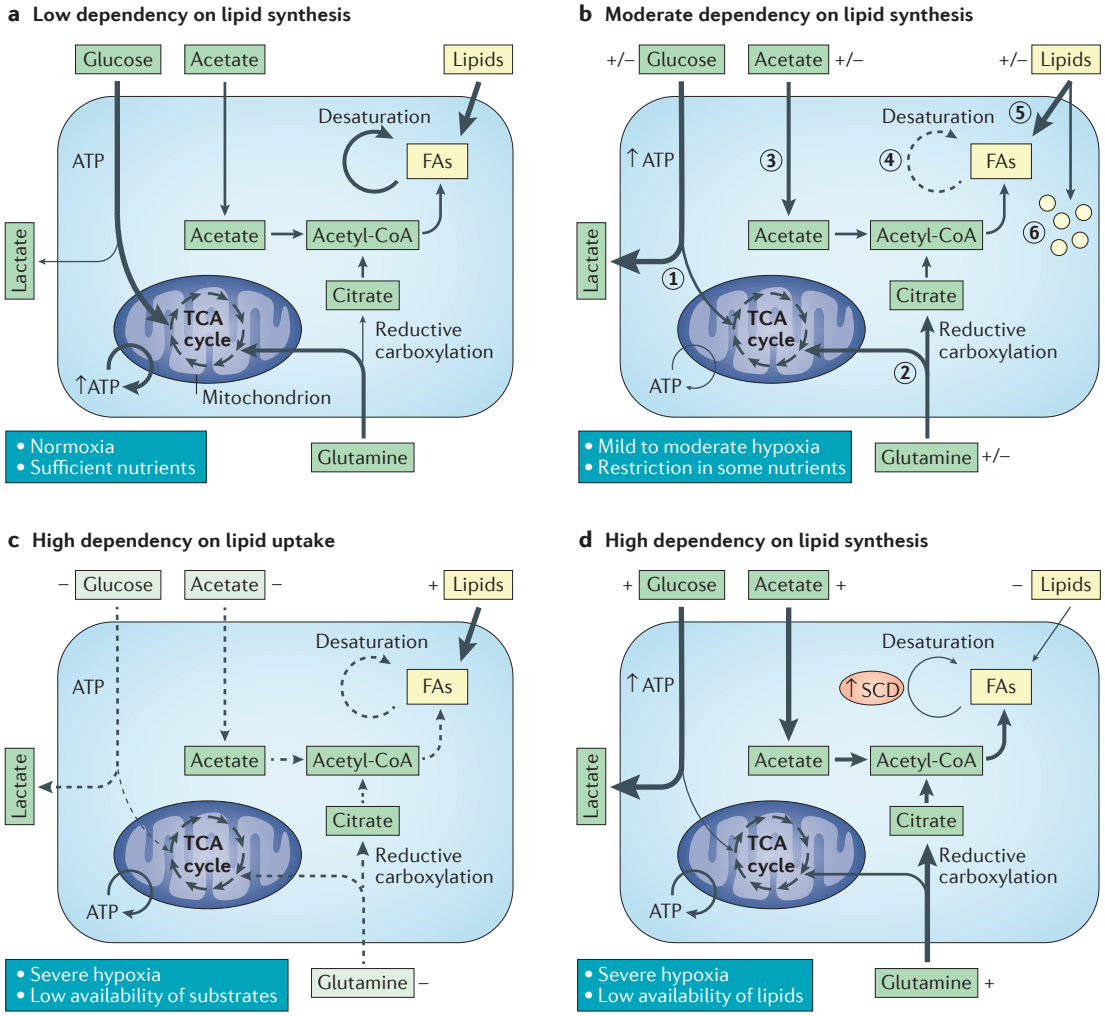


Figure 4 | **Metabolic flexibility in the tumour microenvironment. a** | Cancer cells near a functional blood vessel have sufficient nutrients and oxygen. They may use *de novo* lipid synthesis to convert blood-derived nutrients into fatty acids (FAs) to support rapid cell growth and proliferation. They can also switch to lipid uptake and may therefore not be affected by inhibition of FA biosynthesis. **b** | Cancer cells in areas of mild to moderate hypoxia display moderate dependence on lipid synthesis and uptake. In these conditions, glucose-derived pyruvate is diverted to lactate (step 1). Cells may compensate by switching to alternative carbon sources for FA biosynthesis: glutamine (step 2) or acetate (step 3). As FA desaturation is impaired by oxygen limitation (step 4), cells may depend on the uptake of unsaturated lipids (step 5). Cells may also increase lipid storage for energy provision when oxygen becomes available again (step 6). **c** | In tumour areas of nutrient restriction and severe hypoxia, cancer cells may be completely dependent on exogenous lipid sources. It is not clear, however, whether cancer cells have access to exogenous lipids under these conditions. Release of lipids, for example, from necrotic tumour cells, may provide local lipid sources. **d** | Cancer cells may depend completely on *de novo* FA synthesis if the microenvironment does not provide sufficient lipids. They may also respond by inducing the expression of desaturating enzymes such as stearoyl-CoA desaturase (SCD) to compensate for the reduced activity of these enzymes under hypoxia. Inhibition of lipid synthesis may be effective therapeutically under these conditions. Line thickness represents level of flux through pathway. Dashed lines indicate biosynthetic pathways that are inactive owing to lack of substrates or cofactors. TCA, tricarboxylic acid.

FAs to fuel their metabolism[59]. The constantly changing metabolic landscape of the tumour microenvironment not only depends on blood-derived nutrients, but is also defined by complex interactions between different cell populations. By applying selective pressures on cancer cells, different metabolic niches can give rise to intra-tumour heterogeneity and promote stem cell survival or metastasis formation, which has substantial implications for cancer diagnosis and treatment[60].

Functions of FAs in cancer cells

Given the complex roles of lipids in cellular physiology, it is clear that deregulated FA synthesis must contribute to cancer on many levels, including not only the generation of building blocks for membrane synthesis during cell growth or the provision of substrates for ATP synthesis (BOX 1) but also the regulation of signalling pathways involved in cell proliferation and survival.

FA synthesis and cell growth. Actively proliferating tissues require FAs for the synthesis of structural lipids. Thus, induction of lipid synthesis must be closely connected to cell growth, which is a prerequisite for cell division. Inhibition of FA synthesis, for example by inhibiting ACLY with a small molecule, impaired growth of immortalized haematopoietic cells in response to growth factor stimulation[61]. Moreover, depletion of SREBP blocked the increase in cell size induced by AKT in mammalian cells and reduced cell and organ growth in *Drosophila melanogaster*[30]. However, it is not clear whether this is the consequence of reduced synthesis of membrane phosphoglycerides or involves more indirect effects on signalling pathways that regulate cell growth.

Cardiolipins. Altered FA synthesis and modification can also affect the function of membrane-containing intracellular organelles by altering the composition of specific membrane lipids. Cardiolipins (CLs) are structurally unique phospholipids that are mainly localized to the inner mitochondrial membrane, where they control mitochondrial respiration and function as signalling platforms during the induction of apoptosis[62]. The four acyl chains in CLs undergo constant remodelling through the action of phospholipases and acyltransferases[63], making this lipid class particularly sensitive to changes in cellular FA composition. The length and saturation of CL acyl chains determine the functionality of the inner mitochondrial membrane, particularly the binding of cytochrome *c*[62], which transfers electrons from complex III to complex IV of the electron transport chain (ETC) (FIG. 5a). Changes in FA biosynthesis or uptake in cancer cells can therefore directly affect cellular bioenergetics by modulating ETC activity. Indeed, CL profiles in mitochondria isolated from mouse brain tumours showed marked differences from those taken from normal tissue and correlated with impaired ETC enzyme activity[64].

In contrast to the original Warburg hypothesis[65], many cancers maintain active mitochondria and flux through the ETC[66]. Therefore, interfering with CL synthesis, and hence mitochondrial function, may have therapeutic potential in cancer. Inhibition of acyl-CoA synthetases, also known as FA ligases (ACSLs, ACSMs and ACSFs), families of enzymes required for the activation of intracellular free FAs for subsequent use in biosynthetic reactions, reduces CL production in cancer cells, making them more susceptible to apoptosis[67]. Moreover, inhibition of SCD by a small-molecule inhibitor induced changes in the amounts of specific CL species, reducing cellular respiration and enhancing apoptosis by triggering the release of cytochrome *c* from the mitochondrial membrane[68,69]. Interestingly, inhibition of FA desaturation also increased the sensitivity of cancer cells to chemotherapeutic agents that induce apoptosis via the mitochondrial pathway[68,69], confirming the importance of lipid metabolism for cancer cell survival and drug resistance.

Protein acylation. The abundance and saturation level of cellular FAs also determines the activity of signalling proteins that require acylation for their function. One example is the WNT proteins, which are frequently deregulated in human cancer[70]. WNT proteins are modified by esterification of a palmitoleoyl chain through the activity of the membrane-bound *O*-acyltransferase porcupine (PORCN)[71]. Interestingly, inhibition of PORCN was effective in blocking growth of cancers that depend on excess production and secretion of WNT[72,73]. The preference for Δ9-desaturated acyl chains for WNT acylation implies functional consequences of this modification and explains why SCD is crucial for the activity of the WNT–β-catenin pathway[74]. In addition, unsaturated FAs also regulate β-catenin stability independently of WNT by promoting the polymerization of FAS-associated factor 1 (FAF1), which mediates the interaction between β-catenin and the proteasome[75]. As aberrant activation of the WNT–β-catenin pathway promotes the loss of cell–cell adhesion and disrupts epithelial cell polarity[76], modulation of FA desaturation could contribute to cancer progression and metastasis (FIG. 5b). Other cancer-relevant acylated proteins include SRC and RAS oncoproteins, which are mainly modified through thioesterification with saturated palmitoyl residues[77].

Lipid mediators. Lipids can also function as important signalling molecules. These include the biologically active lipids sphingosine-1-phosphate (S1P)[78] and lysophosphatidic acid (LPA)[79], which control inflammation, cell migration and survival in cancer, and the lipid second messengers DAG[80], inositol-1,4,5-trisphosphate (IP3; also known as Ins(1,4,5)P_3) and PIP3 (REF. 81).These signalling lipids are derived from membrane phospholipids in response to extracellular stimuli (FIG. 5c). As membrane phospholipids are constantly synthesized and remodelled, their acyl-chain composition reflects FA availability within cells. LPA can also be produced in the extracellular space by the secreted phospholipase A2 (PLA2) or the lysophospholipase autotaxin (ATX, also known as ENPP2) (FIG. 5c). LPA signals through autocrine and paracrine mechanisms via G-protein-coupled LPA receptors (LPARs) on the plasma membrane of cancer, immune and endothelial cells, and stimulates proliferation, migration, inflammation and angiogenesis[79]. Interestingly, melanoma cells break down LPA to produce a local gradient that drives their dispersal[82]. The main LPA species in human plasma is 16:0-LPA (that is, LPA containing a 16-carbon palmitoyl group), but species containing mono- and polyunsaturated acyl chains also exist[83]. It was demonstrated that the affinity of LPARs for their ligands depends on the length and degree of saturation of the acyl chain in the LPA molecule[84] and that unsaturated LPA species selectively induce migration of immature dendritic cells in mice[85]. However, little is known about the effect of acyl-chain length or saturation on LPA signalling in cancer. Similarly, analysis of various species of phosphatidylinositols in prostate cancer have revealed distinct changes in acyl-chain composition between benign and malignant tissue[86], but the potential consequences of these changes on signalling processes have not been explored. A study investigating the incorporation of isotope-labelled palmitic acid into different lipid species in cancer cells found that

Acylation
Post-translational covalent attachment of fatty acids to amino acid side-chains of proteins. Common examples are myristoylation and palmitoylation to promote membrane association of proteins.

WNT proteins
A family of secreted glycoproteins involved in tissue homeostasis and organ development. One pathway activated by WNT proteins is β-catenin-induced transcription.

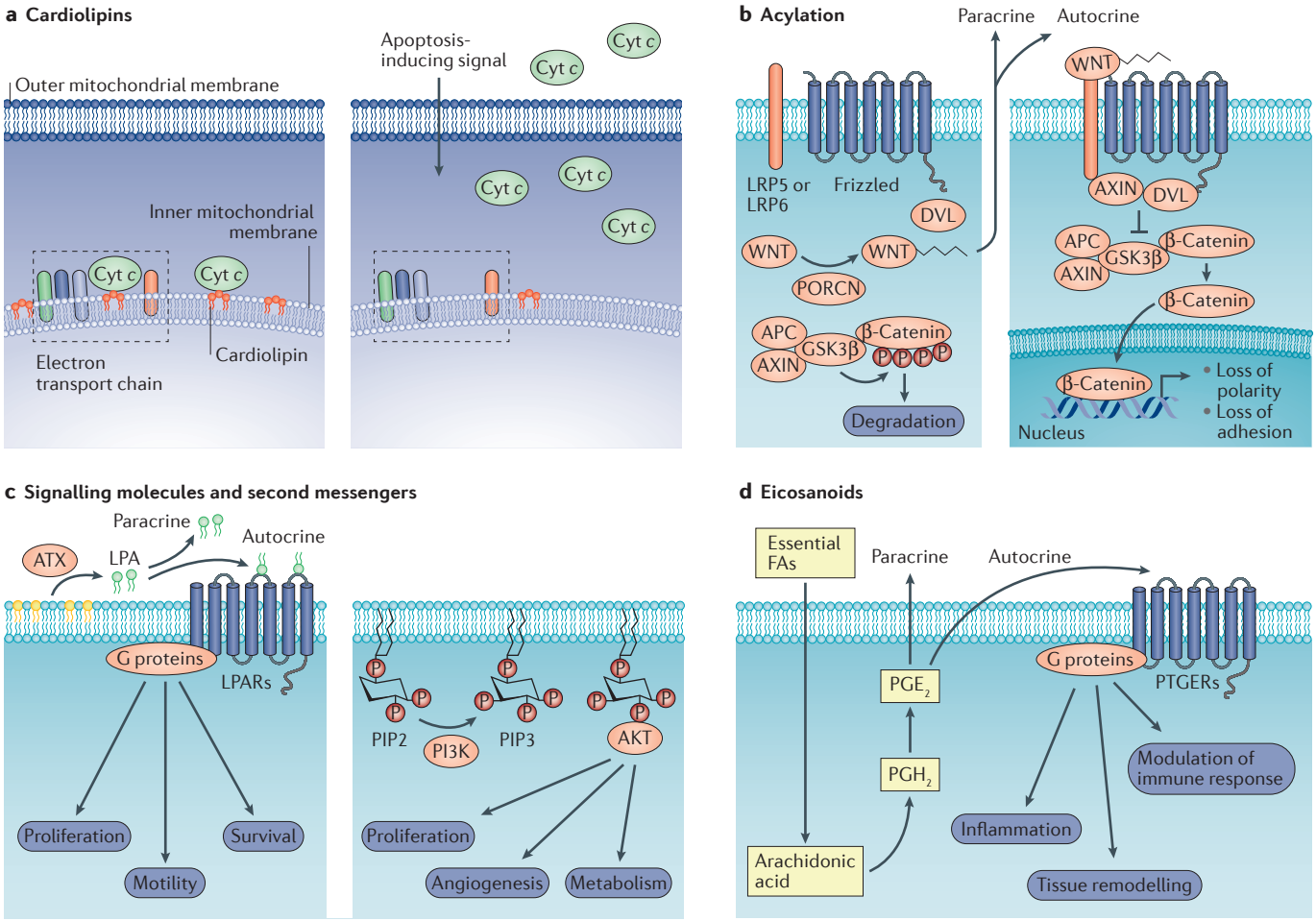


Figure 5 | **Lipids contribute to signalling processes in cancer cells.** Selected mechanisms by which lipids can contribute to intracellular signalling processes and the regulation of apoptosis in cancer cells. **a** | Cardiolipins are important for the function of cytochrome *c* (cyt *c*) as part of the electron transport chain on the inner mitochondrial membrane. Reduced cardiolipin levels weaken the association of cyt *c* with the membrane and can trigger its release from the mitochondria, resulting in enhanced sensitivity towards apoptotic stimuli. **b** | Acylation of WNT promotes the secretion of this protein, thereby enabling paracrine and autocrine signalling by the WNT–β-catenin pathway. **c** | Production of lysophosphatidic acid (LPA) by the extracellular phospholipase autotaxin (ATX) facilitates autocrine signalling via LPA receptors (LPARs), and production of the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3; also known as PtdIns(3,4,5)P_3) activates AKT. **d** | Arachidonic acid is the substrate for the synthesis of prostaglandin E_2 (PGE_2), which binds to prostaglandin E receptors (PTGERs) to regulate inflammation and immune response. APC, adenomatous polyposis coli; DVL, Dishevelled; GSK3β, glycogen synthase kinase 3β; LRP, low-density lipoprotein receptor-related protein; PGH_2, prostaglandin H_2; PIP2, phosphatidylinositol 4,5-bisphosphate (also known as PtdIns(4,5)P_2); PORCN, membrane-bound *O*-acyltransferase porcupine.

aggressive cancer cells rely more heavily on exogenous FAs for the synthesis of signalling lipids[87]. However, it remains to be determined how induction of *de novo* FA synthesis affects composition and functionality of lipid second messengers in cancer cells.

Lipid peroxidation and eicosanoid synthesis. Reactivation of *de novo* FA biosynthesis in cancer changes the overall saturation levels of membrane lipids by increasing the relative amount of saturated and monounsaturated species while polyunsaturated forms, which are mainly derived from dietary lipids, are reduced[88]. This higher saturation level protects cancer cells from ROS, as saturated membrane lipids are less susceptible to peroxidation[89]. However, lipid peroxides also contribute to cellular signalling as intermediates in the synthesis of eicosanoids[54]. Eicosanoids include prostaglandins, leukotrienes and thromboxanes, and are derived from arachidonic acid and eicosapentaenoic acid, two PUFAs produced from the essential linoleic acid or linolenic acid through elongation and desaturation (FIG. 5d). The rate-limiting step in the synthesis of prostaglandins and leukotrienes is catalysed by cyclooxygenase 1 (COX1, also known as PTGS1) and COX2 (also known as PTGS2), and both enzymes are overexpressed in several cancer types[90].

Eicosanoids have multiple modes of action during tumorigenesis, as they regulate inflammation, induce the remodelling of the tumour microenvironment and

Epithelial-to-mesenchymal transition
(EMT). A phenotype that occurs during development as well as in cancer cells. During EMT, epithelial cells acquire mesenchymal traits, including loss of cell–cell contacts and enhanced motility, caused by altered transcription and microRNA regulation of cytoskeletal proteins.

modulate the immune response[90]. The importance of eicosanoids for cancer development is well supported. For example, deletion of *Cox2* in mice attenuates the development of lung, breast and colon cancers[91–93]. One of the direct effects of prostaglandins, specifically prostaglandin E_2 (PGE_2), on tumour cells is the induction of proliferation via activation of the RAS–ERK[94] and the β-catenin pathways in colorectal cancer[95]. PGE_2 also suppresses the activation of anticancer immune pathways but induces tumour-promoting inflammation[96]. However, as eicosanoids produced by tumour cells act in an autocrine and paracrine fashion on several cell types in the tumour microenvironment, it is impossible to define a single mode of action for this class of molecules.

Box 2 | **Involvement of lipids in cancer initiation and progression**

Lipids participate in multiple cellular processes that are crucial for cell transformation, tumour development and disease progression

Tumour initiation

Bioenergetics

- Lipids provide substrates for energy production
- Lipids can be used for energy storage to fuel metabolism after reoxygenation

Membrane synthesis

- Fatty acids (FAs) are substrates for phosphoglyceride and sphingolipid synthesis during cell growth
- Membrane lipids support organelle function (for example, mitochondria)

Signalling

- Lipid modification is required for activity of signalling molecules (for example, acylation of WNT and prenylation of RHO)
- Lipid mediators function as second messengers or ligands for autocrine receptor signalling (for example, phosphatidylinositol-3,4,5-trisphosphate (PIP3; also known as $PtdIns(3,4,5)P_3$) and lysophosphatidic acid (LPA))

Tumour progression and drug resistance

Migration

- Biophysical properties of structural lipids alter membrane fluidity
- Prostaglandin E_2 (PGE_2) production by transforming growth factor-β induces epithelial-to-mesenchymal transition
- Small GTPases are prenylated via the mevalonate pathway

Angiogenesis

- PGE_2 secretion by cancer cells induces blood vessel outgrowth
- Free FAs induce vascular endothelial growth factor (VEGF) expression by binding to and activating peroxisome proliferator-activated receptor-γ (PPARγ)

Immunosuppression

- PGE_2 induces reprogramming of macrophages to the M2 subtype
- Release of PGE_2 blocks the type 1 interferon-dependent innate immune response
- Secretion of linoleic acid causes loss of T helper cells
- Metabolic competition between cancer cells and immune cells restricts immune cell function

Metabolic symbiosis

- Cancer cells induce lipolysis in adipocytes to obtain substrates for energy generation
- Lipids may participate in the exchange of metabolites between different cell populations

Drug resistance

- Lipid composition of the mitochondrial membrane determines chemosensitivity of cancer cells
- Degree of saturation of membrane lipids increases oxidative stress tolerance

FAs in cancer progression

In addition to supporting tumorigenesis, the signalling processes governed by lipids also have important roles during cancer progression and metastasis, the leading cause of cancer-related deaths. Studies into the different processes involved in cell migration and invasion, angiogenesis and escape from immune surveillance have provided insight into the multiple possible connections between FA metabolism and cancer progression (BOX 2).

Cell migration and invasion. Many of the signalling molecules described above promote cell migration, and possibly invasion and metastasis. Increased motility of cancer cells is often attributed to epithelial-to-mesenchymal transition (EMT)[97].

Induction of EMT by transforming growth factor-β (TGFβ) in prostate cancer cells induces the expression of COX2, which enhances cell migration via autocrine PGE_2 signalling[98]. Another study showed that in lung cancer cells, TGFβ signalling inhibits ChREBP leading to reduced *de novo* FA synthesis[99]. In these cells, knockdown of FASN reduced the expression of E-cadherin and increased cell migration and metastasis in a tail vein injection model in mice[99].

It is possible that cancer cells switch from a proliferative state, characterized by high *de novo* lipid biosynthesis and rapid cell growth, to a migratory state, in which FA uptake or the selective release of specific FA species from membrane lipids contributes to the formation of signalling molecules that promote cell migration and invasion. Inhibition of FA biosynthesis during cell migration may also divert potentially scarce nutrients away from anabolic processes and reserve cellular energy stores for motility. During this state, uptake of exogenous lipids could be used to support cellular bioenergetics and to provide lipids for the remodelling of the plasma membrane. This concept is also supported by a study showing that expression of FA translocase (FAT, also known as CD36), a membrane glycoprotein involved in the transport of FAs, correlates with expression of EMT markers in liver cancer[100]. Supplementation with exogenous palmitic or oleic acid decreased E-cadherin expression, and increased cell migration and expression of EMT markers. Moreover, expression of FAT correlated with expression of genes associated with the WNT and TGFβ pathways, two potential activators of EMT. However, as FAT can also activate intracellular signalling processes, including SRC activation, in response to FA binding[101], it is somewhat unclear whether the observed effects indeed require FA uptake.

The induction of EMT requires complex remodelling of cellular lipid composition to facilitate changes in membrane fluidity required for cell migration. Treatment of breast cancer cells with compounds that disrupt a gene expression signature associated with EMT reduced membrane fluidity and blocked migration and lung metastasis formation after tail vein injection in mice[102]. Interestingly, the effect on membrane fluidity was abolished after addition of oleic acid, which disrupts the dense packing of saturated acyl chains. Oleic acid also restored metastasis formation *in vivo*[102], suggesting that monounsaturated FAs promote this crucial step during tumour progression.

Angiogenesis. Metastatic dissemination, as well as primary and metastatic tumour growth, also depends on the induction of angiogenesis[103]. Signalling lipids, including PGE_2, LPA and S1P, have important roles in stimulating vessel outgrowth and recruiting immune cells, particularly macrophages, which promote tumour angiogenesis[104,105]. Endothelial cells selectively use FA degradation not for energy generation, but to generate substrates for nucleotide biosynthesis[106]. Moreover, uptake of exogenous FAs by prostate cancer cells enhances the expression of vascular endothelial growth factor (VEGF) through a mechanism requiring FABP5 and PPARγ (REF. 107). FAs in the tumour microenvironment therefore induce pro-angiogenic signalling and promote proliferation of endothelial cells to provide cancer cells with a growth advantage once new vessels have been established.

Escape from immune surveillance. Cancer cells also evolve the ability to escape immune surveillance, a process called immunoediting. In addition to inhibiting the cytotoxic function of T cells through expression of checkpoint proteins, cancer cells can also reprogramme macrophages to a pro-tumorigenic phenotype. Immunoediting involves complex interactions between cancer and stromal cells that may be modulated by lipid-derived factors[108], such as PGE_2. In cancer cells, PGE_2 generally dampens the immune response, for example, by inducing the release of the immunosuppressive cytokine interleukin-10 (IL-10)[109]. PGE_2 released by cancer cells can also shift tumour-associated macrophages from the tumour-inhibitory M1 to the tumour-promoting M2 phenotype[110]. Moreover, the release of PGE_2 by cancer cells also blocks the initial activation of type I interferon-dependent innate immune cells and establishes a COX2-driven tumour-promoting inflammatory state, and inhibition of COX2 synergizes with antibodies against the immune checkpoint protein programmed cell death protein 1 (PD1, also known as PDCD1)[96].

Cancer cells might also affect the metabolic activity of immune cells. There is evidence that cancer cells compete with immune cells for scarce nutrients within the tumour microenvironment[111]. Whereas T cells switch to glycolysis during activation, induced regulatory T cells and memory T cells rely on lipid oxidation as a major source of energy[112]. It is therefore possible that lipids, in addition to glucose and glutamine, are rate-limiting nutrients in the tumour microenvironment that have to be considered in the context of metabolic competition between different cell types. Metabolites can also be directly involved in the crosstalk between cancer and immune cells. Lactate, for example, is secreted by glycolytic cancer cells and can inhibit the activity of natural killer cells[113]. In addition, breast tumours can release free FAs to block the antitumour activity of cytotoxic T cells[114]. Moreover, secretion of linoleic acid by hepatocytes in non-alcoholic fatty liver disease (NAFLD) induces the selective loss of intrahepatic $CD4^+$ T cells and promotes the development of hepatocellular carcinoma[115]. More detailed analyses of the metabolic interactions between tumour and immune cells are likely to reveal additional modes of regulation.

Non-alcoholic fatty liver disease
(NAFLD). Pathological accumulation of fat in the liver often associated with insulin resistance and the metabolic syndrome.

Metronomic treatment regimens
Therapeutic concept describing the continuous administration of drugs at doses below the maximum tolerated dose.

Therapeutic implications

After early studies demonstrated that activation of *de novo* FA synthesis is specific to cancerous tissues (as compared with normal tissues) in various cancer types (most notably breast and prostate cancer, reviewed in REFS 116,117), substantial efforts have been made to develop strategies to target this pathway for cancer treatment. Although most normal tissues should be protected from the effects of targeting FA synthesis through lipids provided by the bloodstream, dose-limiting toxicity may arise in the liver or adipose tissue. Although metronomic treatment regimens could help to alleviate these problems, strategies that exploit the specific metabolic dependencies of cancer cells are most promising.

FASN as a drug target. Over the past two decades, several different inhibitors of FASN have been developed and evaluated in preclinical studies. Cerulenin, an antifungal antibiotic, inhibits the β-ketoacyl-reductase activity of FASN and both inhibits proliferation and induces apoptosis in cancer cells *in vitro* and *in vivo*[4,118–120]. Similarly, the synthetic compound C75 blocked DNA replication[121], caused apoptosis in several cancer cell lines[119,122–124] and was antitumorigenic in xenograft models of mesothelioma[125] as well as breast[119], renal[126], lung[127] and prostate cancer[128]. C75 also prevented breast cancer development in *HER2* (also known as *ERBB2*)-transgenic mice[129] and increased taxol sensitivity of breast cancer cells *in vitro*[124]. In addition, the plant flavonol epigallocatechin gallate (EGCG), found in green tea, which is currently undergoing clinical evaluation for anticancer activity, can inhibit FASN, among other targets[130].

A major setback in targeting FASN in cancer was the observation that C75 reduces food intake and induces weight loss in mice by increasing levels of malonyl-CoA[131] and by inducing the expression of hypothalamic neuropeptides, which regulate energy intake and expenditure[132]. It was later shown that systemic treatment with C75 increases levels of malonyl-CoA in the hypothalamus, but decreases levels of this metabolite in peripheral muscle, resulting in activation of β-oxidation and excessive energy expenditure, thereby exacerbating the detrimental effect of this drug[133]. The subsequent development and testing of novel compounds that do not have systemic effects resulted in the first FASN inhibitor recently entering clinical trials (TABLE 1).

In addition to chemical inhibition, several studies have applied genetic approaches to target FA synthesis in cancer. These included experiments using RNA interference (RNAi) targeting FASN in cultured human cancer cells, and studies in xenograft tumours and mouse models of human cancer (Supplementary information S1 (table)). Moreover, deletion of *Fasn* in mice abolished AKT-induced development of hepatocellular carcinoma[134]. Although the results of these studies are certainly encouraging, the problem of potential side effects of targeting FASN still remains. FASN was shown to be essential for adult neuronal stem cell function[135], raising additional concerns about adverse responses. However, an unsolved question is the potential metabolic flexibility of cancer cells, which could lead to rapid

Table 1 | **Fatty acid synthesis inhibitors in preclinical and clinical development**

Compound	Mechanism of action	Preclinical model or clinical trial	Effect	Refs
FASN				
TVB-2640	NA	Refractory solid tumours, phase I	Ongoing trial	197
TVB-3166	Inhibition of the β-ketoacyl-reductase activity	Multiple cancer cell lines, pancreatic cancer xenografts	Inhibition of proliferation and reduction in tumour growth	40,198
GSK2194069	Inhibition of the β-ketoacyl-reductase activity	Prostate cancer xenografts	Reduction of tumour volume and reduction of acetate uptake	199
C93	Inhibition of the β-ketoacyl-synthase activity	Ovarian cancer and non-small-cell lung cancer cell lines and xenografts	Cytotoxicity, AMPK activation and inhibition of tumour growth; no effect on body weight	200,201
FAS31	Not known	Ovarian cancer xenograft	Tumour reduction; no effect on body weight	202
C247	Not known	*HER2* transgenic mice (breast cancer model); non-small-cell lung cancer cell lines and xenografts	Chemoprevention (breast), inhibition of cell proliferation and reduction of tumour growth; no effect on body weight	129,203
C75	Inhibition of the β-ketoacyl-synthase activity	Colon cancer cell lines	Inhibition of DNA replication and induction of apoptosis	122
		Breast, ovarian, lung, renal, prostate and mesothelioma cancer cell lines and xenografts	Accumulation of malonyl-CoA and inhibition of tumour growth (breast and prostate)	119,120,123–128
		HER2 transgenic mice	Chemoprevention and increased taxol sensitivity	129
		Intracerebroventricular treatment in mice	Anorexia	195
Cerulenin	Irreversible inhibition of β-ketoacyl-synthase activity	Ovarian cancer and breast cancer cell lines and xenografts	Inhibition of proliferation, induction of apoptosis, inhibition of tumour growth, accumulation of malonyl-CoA and inhibition of HER2 overexpression (breast)	4,118–120,204
Orlistat	Inhibition of thioesterase domain	Prostate cancer and melanoma cell lines and xenografts	Induction of apoptosis, reduction of tumour growth and inhibition of metastasis (melanoma)	205,206
Triclosan	Inhibition of enoyl-ACP reductase domain	Prostate cancer cell lines	Induction of apoptosis and induction of senescence	207,208
		Breast cancer cell lines and xenografts	Enhanced tumour progression	
Other targets				
TOFA	Inhibition of ACCs	Lung, colon and breast cancer cell lines	Induction of apoptosis	119,144
Soraphen A	Inhibition of ACCs	Prostate cancer cell lines	Induction of apoptosis	209
SB-204990	Inhibition of ACLY	Lung, prostate and ovarian cancer cell lines and xenografts	Inhibition of tumour growth in cells dependent on glycolytic metabolism	61,136
Triacscin C	Inhibition of acyl-CoA synthetases	Multiple cancer cell lines and lung cancer xenograft	Inhibition of tumour growth and induction of apoptosis in p53 defective cell lines	67
Etomoxir	Inhibition of CPT1	Leukaemia and myeloma cell lines	Inhibition of proliferation	210,211
Perhexiline	Inhibition of CPT1	Primary leukaemia cells and *TCL1* transgenic mice	Loss of cell viability and reduction in tumour growth	212
BZ36	Inhibition of SCD	Prostate cancer cell lines and xenografts	Decrease in proliferation and inhibition of tumour growth and AKT signalling	170

Table 1 (cont.) | **Fatty acid synthesis inhibitors in preclinical and clinical development**

Compound	Mechanism of action	Preclinical model or clinical trial	Effect	Refs
Other targets (cont.)				
A939572	Inhibition of SCD	Breast and prostate cancer cell lines, and prostate cancer xenografts; lung cancer and squamous carcinoma cell lines, and patient-derived gastric cancer xenografts	Inhibition of proliferation in reduced serum conditions, and reduction of tumour growth	69,169
		Clear cell renal cell carcinoma cell lines and xenografts	Cooperative effect on tumour growth with temsirolimus	213
Fatostatin	Inhibition of SREBP–SCAP interaction	Prostate cancer cell lines and xenografts	Inhibition of proliferation and reduction of androgen receptor expression; cooperative toxicity with docetaxel	159,160
Betulin	Inhibition of SREBP–SCAP interaction	Multiple cancer cell lines	Inhibition of proliferation	Reviewed in 162

ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; ACP, acyl carrier protein; AMPK, AMP-activated protein kinase; CPT1, carnitine palmitoyltransferase 1; FASN, fatty acid synthase; NA, not available; SCAP, SREBP cleavage-activating protein; SCD, stearoyl-CoA desaturase; SREBP, sterol regulatory element binding protein; *TCL1*, T-cell leukaemia/lymphoma 1; TOFA, 5-tetradecyl-oxy-2-furoic acid.

adaptation and resistance. For example, cancer cells could switch from *de novo* FA synthesis to FA uptake in the presence of FASN inhibitors. Moreover, as inhibition of FASN can induce EMT[99], targeting this enzyme could even promote the development of metastases. Therefore, current efforts are concentrating on identifying the exact role of altered lipid metabolism in cancer to find alternative strategies or additional targets that could induce selective toxicity in cancer cells.

Widening the search: additional targets in FA synthesis. Other lipid metabolism enzymes might also be therapeutic targets in cancer[6]. For example, depletion or inhibition of ACLY efficiently blocked cancer cell growth and tumour formation[61,136,137]. However, it was later shown that the acetyl-CoA produced by nuclear ACLY also contributes to histone acetylation and may therefore modulate cancer cell growth on multiple levels[138]. Similarly, ACSS2-mediated production of acetyl-CoA from acetate contributes to FA biosynthesis in hypoxic cancer cells[45,139] and is essential for cancer cell survival under metabolically compromised conditions *in vitro* as well as in xenograft tumours and genetic mouse models of cancer[139–141]. Interestingly, acetate was also shown to be a major bioenergetic substrate for tumours in patients with glioblastoma or brain metastases of other cancer types[142]. The specific role of ACSS2 in cells that are hypoxic or metabolically stressed opens a therapeutic window in which ACSS2 could be specifically toxic only to tumours. Acetyl-CoA synthesis represents a central node in the metabolic network and its multiple connections to cancer-relevant processes are discussed by Gottlieb and colleagues in this Focus issue[143].

Another strategy to efficiently reduce FA provision in cancer cells is the inhibition of ACCs. In contrast to FASN blockade, which leads to the accumulation of malonyl-CoA[119], an efficient inhibitor of β-oxidation (see BOX 1), inhibition of ACCs would block FA synthesis but simultaneously induce β-oxidation, resulting in more severe lipid depletion. Targeting of ACCs by chemical inhibition[144] or silencing limits cancer cell proliferation[145,146]. However, silencing of *ACC1* or *ACC2* reduced oxidative stress in cancer cells and promoted xenograft growth[147], suggesting that inhibition of FA synthesis could also promote tumorigenesis by limiting cellular NADPH demand and restoring redox balance.

Targeting SREBPs. Given the importance of lipids as membrane components, increased lipid biosynthesis must arise from oncogenic pathways that promote the rapid proliferation in cancer. Targeting SREBP, or other upstream regulators of lipid synthesis, could therefore be an efficient strategy to halt tumour growth. One of the consequences of silencing of *SREBP1* and *SREBP2* is altered cellular lipid composition, with a marked reduction in monounsaturated species and concomitant increase in saturated forms[148,149]. This results in mitochondrial dysfunction and oxidative stress, leading to ER stress and induction of the unfolded protein response (UPR) pathway[148,149]. Interestingly, expression of myristoylated AKT in immortalized human epithelial cells increased their sensitivity towards SREBP silencing[148], suggesting that oncogene activation enhances cellular demand for monounsaturated lipids. In addition, monounsaturated FAs were essential to support proliferation and prevent ER stress in mouse embryonic fibroblasts (MEFs) cultured in hypoxic conditions with reduced glucose availability (conditions resembling tumour-like stress) when mTORC1 was activated[150]. The connection between mTORC1 and SREBP and the control of ER homeostasis during proliferation and cell growth was also confirmed in *D. melanogaster* cells[151]. Together, these studies demonstrate that protein and lipid synthesis have to be regulated in a concerted manner during cell growth and proliferation (Supplementary information S2 (figure)).

Interestingly, nuclear localization of SREBP1 was found to correlate with increased levels of FASN and ACC in glioblastomas displaying activating mutations of the epithelial growth factor receptor variant III (EGFRvIII)[152]. Surprisingly, activation of SREBP1 by EGFRvIII seemed

Unfolded protein response (UPR) pathway
A stress response pathway activated upon accumulation of misfolded proteins in the lumen of the endoplasmic reticulum.

to be insensitive to mTORC1 inhibition, suggesting alternative routing of the pathway. Nevertheless, combined inhibition of FASN and 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (HMGCR), the rate-limiting enzyme in isoprenoid synthesis, reduced xenograft growth of EGFRvIII-overexpressing glioblastoma cells[152]. It was later shown that EGFR activation also increases glucose uptake in glioblastoma cells, leading to enhanced *N*-glycosylation of SCAP. This modification triggers the dissociation of the inhibitory factor INSIG, thereby promoting ER–Golgi translocation of the SREBP–SCAP complex and enhancing lipogenesis. Consequently, expression of wild-type but not glycosylation-deficient SCAP promoted the ability of glioblastoma cells to form large tumours[153]. As induction of glucose uptake in response to growth factor signalling is mediated by AKT-dependent translocation of glucose transporters, induction of SCAP glycosylation can be added as another mechanism for the regulation of SREBP activity downstream of AKT (FIG. 3d). Additional lines of investigation established that RNAi-mediated silencing of SREBP1 or SREBP2 prevents xenograft growth of glioblastoma cells that do not carry EGFR mutations, but in which the AKT pathway is activated through different mechanisms[148,149]. Moreover, it was shown that SREBP1 controls a transcriptional programme associated with poor survival in glioblastoma and that it supports cell survival under lipid- and oxygen-deprived conditions[52].

Together with the results discussed above, these studies provide strong evidence that SREBPs have important roles in this cancer type. However, targeting SREBPs directly is challenging, as transcription factors often cannot be inhibited by small molecules. One strategy is the targeting of upstream regulators of SREBPs, the liver X receptors, LXRα and LXRβ (also known as NR1H3 and NR1H2, respectively), which form heterodimers with the retinoid X receptor-α (RXRα) in the presence of oxysterols, mono-oxygenated derivatives of cholesterol. LXRs induce the expression of enzymes involved in glycolysis and lipogenesis by activating SREBP1c or ChREBP. However, LXRs also limit cholesterol uptake by inducing the proteolytic degradation of LDLR[154]. So far, strategies to target LXRs in cancer have mainly considered their activation via agonists, which inhibit tumorigenesis in several *in vitro* and *in vivo* systems (REF. 155 and references therein). For example, treatment with the LXR agonist GW3965 increases cholesterol efflux and blocks xenograft growth of EGFRvIII-expressing glioblastoma cells[156]. More recently, however, it was shown that inhibition of LXR signalling by a small molecule induces apoptosis in a wide variety of cancer cells by blocking the expression of enzymes involved in glycolysis and FA biosynthesis[157].

Another strategy is the development of inhibitors that target the SREBP–SCAP interaction to keep the transcription factors in their inactive state. Two such compounds have been identified. One of these, fatostatin[158], has been shown to reduce the growth of prostate cancer xenografts[159,160]. The other is the natural compound betulin, which improved diet-induced obesity in mice by inhibiting SREBP activation[161]. Although betulin has shown antiproliferative effects on cancer cell lines[162], this activity has not been connected to SREBP function. Adverse effects of targeting this pathway are currently unknown. However, although germline deletion of *Srebp1* causes partial lethality, liver-specific deletion of *Scap* in adult mice altered insulin response but did not affect weight gain or cause poor health[163]. Specific strategies, such as the recent advance of phthalimide conjugates, which selectively induce the degradation of target proteins[164], will increase possibilities of targeting these factors.

Targeting FA elongation and desaturation. Other processes that have received attention for possible therapeutic targeting are FA elongation and desaturation. For example, human lung squamous cell carcinomas (SCCs) show increased abundance of long-chain phospholipids, and inhibition of the FA elongase 6 (ELOVL6) decreased the ability of SCC cells to grow as xenograft tumours[165]. Moreover, inhibition of the desaturase SCD efficiently blocked cancer cell proliferation by selectively depleting monounsaturated FAs[69,166–169]. This inhibited oncogenic signalling pathways[170], activated AMP-activated protein kinase (AMPK)[168] and increased sensitivity towards chemotherapies[68,69]. Interestingly, these studies found that SCD inhibition only blocks cancer cell survival *in vitro* in the absence of exogenous lipids, particularly oleic acid. Nevertheless, silencing of *SCD* reduced tumours in xenograft models of lung[171], gastric[169] and liver cancer[172] and prevented orthotopic growth of prostate cancer cells *in vivo*[69], confirming that unsaturated lipids are indeed limited within the tumour microenvironment.

Drug resistance and disease progression. One of the main causes of cancer-associated mortality is the development of therapy resistance that inevitably leads to treatment failure and disease progression[173]. Alterations in lipid metabolism can affect drug resistance. Several studies have demonstrated that inhibition of FASN increases the chemosensitivity of breast cancer cells[174–176]. As already described above, inhibition of FA desaturation increases the sensitivity of cancer cells towards apoptosis-inducing drugs by changing CL synthesis[68,69]. In addition, some drugs, in particular antiangiogenic therapies, can also induce rapid disease progression after treatment withdrawal, at least in preclinical mouse models of cancer, raising concerns about their use in patients[177]. A potential role of lipid metabolism in this process was recently reported in tumours following the withdrawal of the angiogenesis inhibitor sunitinib[178]. Xenograft tumours of human breast and colon cancer cells that had progressed following sunitinib withdrawal had increased FA biosynthesis, and pharmacological inhibition or knockdown of FASN reduced tumour regrowth and metastasis after sunitinib withdrawal[178]. Although the underlying causes for this metabolic shift are still unclear, it may offer leads for the development of strategies for combination treatments with antiangiogenic drugs and inhibitors of FA synthesis.

Summary and future directions

Work over the past two decades has clearly established altered lipid metabolism as an important metabolic phenotype of cancer cells. Blocking lipid provision in

Imaging mass spectrometry (IMS). Technique to visualize the spatial distribution of metabolites, biomarkers or proteins in a biological sample, such as a tissue section.

cancer cells should therefore have dramatic consequences for cancer cell bioenergetics, membrane biosynthesis and intracellular signalling processes. Moreover, altered lipid availability can also affect cancer cell migration, induction of angiogenesis, metabolic symbiosis, escape from immune surveillance and drug resistance in cancer. Availability of FAs in the blood and peripheral tissues depends on lifestyle and diet and is likely to be altered in patients who are obese or have metabolic syndrome[179]. Thus, effects of FAs on tumorigenic processes may provide mechanistic insight into the increased cancer risk associated with these conditions.

It is therefore somewhat surprising that only one targeted compound aimed at this pathway has so far entered clinical trials. One reason for this could be the difficulty of selectively inhibiting lipid metabolism in cancer cells without major systemic effects. Another limitation comes from the possibility of metabolic flexibility of cancer cells, which may rapidly switch from *de novo* synthesis to lipid uptake in the presence of inhibitory compounds. It is also clear that lipid metabolism in cancer has to be studied under conditions that faithfully represent the conditions of the tumour microenvironment. Many effects of inhibition of FA synthesis are only revealed under experimental conditions of reduced availability of exogenous lipids. However, the essentiality of acetate synthesis and FA desaturation initially identified under these conditions *in vitro* was also retained *in vivo*, at least in preclinical cancer models[69,139]. In this context, it is essential to establish the availability of exogenous lipids within live tumours. Label-free imaging techniques, such as Raman spectroscopy or imaging mass spectrometry (IMS) may offer new insights into the lipid composition of tumours. Moreover, functional imaging of suitable tracers by positron emission tomography (PET) may be used to determine whether tumours rely on *de novo* synthesis or uptake to fulfil their FA demand. For example, PET-imaging using [1-^{11}C]acetate demonstrated FA biosynthesis in lung tumours induced by oncogenic KRAS (KRAS-G12D) in mice[180]. It would be interesting to conduct similar experiments using derivatives of palmitate, primarily used to analyse myocardial metabolism[181]. These techniques need to be applied to establish target inhibition *in vivo* and identify potential resistance mechanisms. However, given the complexity of cellular lipid species and the dynamic nature of their synthesis, remodelling and breakdown, targeting this aspect of cancer cell metabolism remains challenging.

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Competing interests statement
The authors declare no competing interests.

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CORRIGENDUM

From Krebs to clinic: glutamine metabolism to cancer therapy

Brian J. Altman, Zachary E. Stine and Chi V. Dang

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On page 619 of the above article tyrosine was incorrectly referred to as an essential amino acid; this has now been corrected to tryptophan.