The multifaceted roles of fatty acid synthesis in cancer

Florian Röhrig¹,² and Almut Schulze¹,²

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.

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)P₃), 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 liver³. 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 synthesis⁴. Several decades later, fatty acid synthase (FASN) was identified as the tumour antigen OA-519 in aggressive breast cancer⁴. Numerous studies have since confirmed the importance of FA biosynthesis for cancer cell growth and survival⁵,⁶ (FIG. 1).

The modular nature of lipids, particularly those containing several FAs, determines the enormous structural complexity in this class of molecules⁷. 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 breast⁸. Expression of FASN is also found in proliferating fetal tissues⁹, 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 synthesis¹⁰ 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
FOCUS ON TUMOUR METABOLISM

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. This process generates citrate, which is cleaved into acetyl-CoA and oxaloacetate by ATP-citrate lyase (ACLY) in the cytoplasm. Malonyl-CoA is then formed by acetyl-CoA carboxylases (ACCs, also known as ACACs), enzymes that are highly regulated by phosphorylation and allosteric regulation. 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 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. 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 SREBP1 gene, and SREBP2, the product of the SREBP2 gene (REF. 16). SREBPs bind to sterol regulatory elements (SREs) and some E-box sequences in the promoters of their target genes. These target genes also encode enzymes of the cholesterol biosynthesis pathway, discussed in greater detail by Mullen et al. 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 co-factor 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). SREBP1 has also been connected to the one-carbon cycle, 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. 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). 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 storage of the SREBP-SCAP complex in the ER (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, 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. 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. SREBP target genes were also found to be a major component of the transcriptional response to mTORC1 activation, 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 by ACLY. 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 carboxylase; ACSS2, cytoplasmic acetyl-CoA synthetase; COX, cyclooxygenase; GLS, glutaminase; GLUT, glucose transporter; G3P, glyceraldehyde-3-phosphate; G6P, glucose-6-phosphate; HK, hypoxia-inducible factor; HK, hexokinase; IDH, isocitrate dehydrogenase; MCT, monocarboxylate transporter; ME, malic enzyme; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; SLC1A5, solute carrier family 1 member 5; TCA, tricarboxylic acid.
**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.

Generating energy from stored TAGs requires initial cleavage of acyl chains from the glycerol backbone through a process called lipolysis. 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 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.

β-Oxidation generates energy at several steps: the step-wise shortening of acyl-CoA generates one molecule of FADH₂ and NADH for every 2-carbon unit released. Each acetyl-CoA molecule then yields 3 molecules of NADH, 1 molecule of FADH₂, 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) 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. 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. Targeting this pathway may limit the metabolic flexibility of cancer cells and should be considered as a strategy for cancer treatment.

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**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 factors or also by the tumour microenvironment.
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. 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 inhibited41. 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 carboxylation42,43, and the direct synthesis of acetyl-CoA from acetate by cytoplasmic acetyl-CoA synthetase (ACSS2)44.

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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 COPII-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.
**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. 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). Upon re-oxygenation, cells used these stored lipids for energy production and antioxidant defence. This increased the ability of the cells to survive 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.

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. 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 ([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. 4](#)b). 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. 4](#)c). 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. 4](#)d). 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. 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. 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 O2, the synthesis of monounsaturated FAs is compromised under severe hypoxia. However, expression of SCD was induced in response to intermittent hypoxia in mice and after exposure to lipid- and oxygen-deprived conditions in glioblastoma cells, 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. These enzymes are involved in the generation of polyunsaturated FAs (PUFAs), which are important modulators of inflammation and immune responses.

**Metabolic symbiosis.** It is well established that systemic mobilization of lipids from adipose tissue fuels tumour growth during cancer cachexia. 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. Metabolite transfer has also been observed between cancer cells and cancer-associated fibroblasts (CAFAs) ([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 (BOX 1). Moreover, leukaemia stem cells evade chemotherapy by migrating to gonadal fat tissue, where they use adipose-derived
FAs to fuel their metabolism. 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.

**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.

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**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.
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. 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. 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. The four acyl chains in CLs undergo constant remodelling through the action of phospholipases and acyltransferases, 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, 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.

In contrast to the original Warburg hypothesis, cancer cells maintain active mitochondria and flux through the ETC. 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. 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. Interestingly, inhibition of FA desaturation also increased the sensitivity of cancer cells to chemotherapeutic agents that induce apoptosis via the mitochondrial pathway, confirming the importance of lipid metabolism for cancer cell survival and drug resistance.

Lipid mediators. Lipids can also function as important signalling molecules. These include the biologically active lipids sphingosine-1-phosphate (SIP) and lysophosphatidic acid (LPA), which control inflammation, cell migration and survival in cancer, and the lipid second messengers DAG, inositol-1,4,5-trisphosphate (IP3; also known as Ins(1,4,5)P3) and PIP3. These signalling lipids are derived from membrane phospholipids in response to extracellular stimuli. As membrane phospholipids are continuously 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). 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.

Interestingly, melanoma cells break down LPA to produce a local gradient that drives their dispersal. 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. 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 and that unsaturated LPA species selectively induce migration of immature dendritic cells in mice. 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, 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...
aggressive cancer cells rely more heavily on exogenous FAs for the synthesis of signalling lipids. 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. This higher saturation level protects cancer cells from ROS, as saturated membrane lipids are less susceptible to peroxidation.

However, lipid peroxides also contribute to cellular signalling as intermediates in the synthesis of eicosanoids. 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.

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

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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. 

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<th>a Cardiolipins</th>
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**b Acylation**

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<td>LRP5 or LRP6</td>
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<td>APC AXIN</td>
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<td>Degradation Nucleus</td>
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**c Signalling molecules and second messengers**

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<td>Motility</td>
<td>Angiogenesis</td>
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**d Eicosanoids**

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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. 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. One of the direct effects of prostaglandins, specifically prostaglandin E2 (PGE2), on tumour cells is the induction of proliferation via activation of the RAS–ERK and the β-catenin pathways in colorectal cancer. PGE2 also suppresses the activation of anticancer immune pathways but induces tumour-promoting inflammation. 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)P3) and lysophosphatidic acid (LPA))

**Tumour progression and drug resistance**

**Migration**

- Biophysical properties of structural lipids alter membrane fluidity
- Prostaglandin E2 (PGE2) production by transforming growth factor-β induces epithelial-to-mesenchymal transition
- Small GTPases are prenylated via the mevalonate pathway

**Angiogenesis**

- PGE2 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**

- PGE2 induces reprogramming of macrophages to the M2 subtype
- Release of PGE2 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).

Induction of EMT by transforming growth factor-β (TGFβ) in prostate cancer cells induces the expression of COX2, which enhances cell migration via autocrine PGE2 signalling. Another study showed that in lung cancer cells, TGFβ signalling inhibits STAT3 leading to reduced de novo FA synthesis. 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.

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. 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, 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. 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, 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. Signalling lipids, including PGE₂, LPA and S1P, have important roles in stimulating vessel outgrowth and recruiting immune cells, particularly macrophages, which promote tumour angiogenesis. Endothelial cells selectively use FA degradation not for energy generation, but to generate substrates for nucleotide biosynthesis. 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. 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 cytokine 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. Toxins function to inhibit the cyto toxic activity of cytotoxic 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, such as PGE₂. In cancer cells, PGE₂ generally dampens the immune response, for example, by inducing the release of the immunosuppressive cytokine interleukin-10 (IL-10). PGE₂ released by cancer cells can also shift tumour-associated macrophages from the tumour-inhibitory M1 to the tumour-promoting M2 phenotype. Moreover, the release of PGE₂ by cancer cells also blocks the initial activation of type I interferon-dependent innate immune cells and establishes a COX2-driven tumour-provocative inflammatory state, and inhibition of COX2 synergises with antibodies against the immune checkpoint protein programmed cell death protein 1 (PD1, also known as PDCD1).

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. 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. 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. In addition, breast tumours can release free FAs to block the anti-tumour activity of cytokotic T cells. 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. More detailed analyses of the metabolic interactions between tumour and immune cells are likely to reveal additional modes of regulation.

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 references 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. Similarly, the synthetic compound C75 blocked DNA replication, caused apoptosis in several cancer cell lines and was antitumorigenic in xenograft models of mesothelioma and as breast, renal, lung and prostate cancer. C75 also prevented breast cancer development in HER2 (also known as ERBB2)-transgenic mice and increased taxol sensitivity of breast cancer cells in vitro. 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.

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 and by inducing the expression of hypothalamic neuropeptides, which regulate energy intake and expenditure. 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. 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. In a recent study, FASN expression was increased in a panel of breast cancer cell lines, and treatment with an FASN inhibitor resulted in decreased tumour growth in vivo. Furthermore, deletion of Fasn in mice abolished AKT-induced development of hepatocellular carcinoma. 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, raising additional concerns about adverse responses. However, an unsolved question is the potential metabolic flexibility of cancer cells, which could lead to rapid

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

Clear cell renal cell carcinoma cell lines and xenografts

Prostate cancer cell lines and xenografts

Multiple cancer cell lines

Fatostatin

Inhibition of SREBP–SCAP interaction

Prostate cancer cell lines and xenografts

Multiple cancer cell lines

Betulin

Inhibition of SREBP–SCAP interaction

Multiple cancer cell lines

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

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

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; SCAF, SREBP cleavage-activating protein; SCD, stearoyl-CoA desaturase; SREBP, sterol regulatory element binding protein; TCL1, T-cell leukaemia/lymphoma 1; TOFA, 5-tetradecyl-oxo-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 EMT79, 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 cancer9. For example, depletion or inhibition of ACLY efficiently blocked cancer cell growth and tumour formation81,136,137. 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 levels138. Similarly, ACS2-mediated production of acetyl-CoA from acetate contributes to FA biosynthesis in hypoxic cancer cells65,139 and is essential for cancer cell survival under metabolically compromised conditions in vitro as well as in xenograft tumours and genetic mouse models of cancer139–141. Interestingly, acetate was also shown to be a major bioenergetic substrate for tumours in patients with glioblastoma or brain metastases of other cancer types142. The specific role of ACS2 in cells that are hypoxic or metabolically stressed opens a therapeutic window in which ACS2 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 issue143.

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-CoA119, 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 inhibition144 or silencing limits cancer cell proliferation145,146. However, silencing of ACC1 or ACC2 reduced oxidative stress in cancer cells and promoted xenograft growth147, 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 forms148,149. This results in mitochondrial dysfunction and oxidative stress, leading to ER stress and induction of the unfolded protein response (UPR) pathway148,149. Interestingly, expression of myristoylated AKT in immortalized human epithelial cells increased their sensitivity towards SREBP silencing148, 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 activated149. The connection between mTORC1 and SREBP and the control of ER homeostasis during proliferation and cell growth was also confirmed in D. melanogaster cells151. 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...
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Imaging mass spectrometry (IMS). Technique to visualize the spatial distribution of metabolites, biomarkers or proteins in a biological sample, such as a tissue section.


2. Medes, G., Thomas, A. & Weinhouse, S. Metabolism of neoplastic tissue. A study of lipid synthesis in neoplastic tissue slices in vitro. Cancer Res. 13, 27–29 (1953). This study was the first to determine lipid synthesis in neoplastic tissue.


27. Porto, T. M. et al. SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth. Cell Metab. 8, 226–236 (2008). This study was the first to demonstrate that SREBP is regulated by mTORC1 and contributes to cell growth.


29. Peterson, T. R. et al. mTORC1 complex 1 regulates lipin 1 localization to control the SREBP pathway. Cell 146, 408–420 (2011). This study implicated LIPIN1 in the regulation of SREBP by mTORC1.

30. Han, J. et al. The CREB coactivator CRTC2 controls hepatic lipid metabolism by regulating SREBP1. Nature 524, 245–246 (2015). This study showed regulation of SREBP1 processing by mTORC1 through phosphorylation of CRTC2.


33. Bengoechea-Alorino, M. T. & Erickson, J. A. Phosphorylation cascade controls the degradation of active SREBP1. J. Biol. Chem. 284, 5885–5895 (2009). References 35 and 36 demonstrated that the stability of mature SREBP is controlled by GSK3-dependent phosphorylation and ubiquitination by the FBW7 ubiquitin ligase.


This study demonstrated that induction of lipid synthesis is essential for premetastatic formation and survival of transformed cells. The effect of MondoA repression was rescued by oleic acid, confirming the importance of monounsaturated FAs for cancer cells.

This study provided an elegant example of lipid storage by hypoxic cells and selectivity take up monounsaturated lipids.


This study established lipid storage by hypoxic cells in energy provision after reoxygenation.


This study connected cholesterol esterification to maintain SREBP activity with aggressive behaviour of prostate cancer.


This study provided an elegant example of metabolic symbiosis of cancer cells and adipocytes.
This study provided evidence of the competition between fatty acid synthase and immune cells for nutrients within the tumor microenvironment.

This study demonstrated that FASN is highly active in proliferating adult neural stem cell progenitors.

This study provided evidence of the competition between fatty acid synthase and immune cells for nutrients within the tumor microenvironment.

Increased fatty acid synthase is a carcinogenic antigen (oncogenic antigen-519) synergistically inhibits cytotoxic stress.

The increased expression of FASN is associated with progression of hepatocellular carcinoma in mice and lipogenesis.

By activating SREBP-1c, FAS acts as a tumor promoter.

It also enhanced glycosylation of SCAP. It also enhanced glycosylation of SCAP.
FOCUS ON TUMOUR METABOLISM

178. Soumi, N. E. et al. Blocking lipid synthesis overcomes tumor regrowth and metastasis after antiangiogenic therapy withdrawal. Cell Metab. 20, 280–294 (2014). This study suggested that inhibition of lipid synthesis may prevent disease progression following antiangiogenic therapy.

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The authors thank B. Peck for helpful discussions and all members of the Schulze laboratory for critical reading of the manuscript. We also wish to acknowledge for the numerous important studies in the field of lipid metabolism in cancer that we could not cite owing to space limitations.

Competing interests statement
The authors declare no competing interests.

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SUPPLEMENTARY INFORMATION
See online article: [S1 table] [S2 figure]
ALL LINKS ARE ACTIVE IN THE ONLINE PDF

CORRIGENDUM
From Krebs to clinic: glutamine metabolism to cancer therapy
Brian J. Altman, Zachary E. Stone and Chi V. Dang
On page 619 of the above article tyrosine was incorrectly referred to as an essential amino acid; this has now been corrected to tryptophan.