

# 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,  $\beta$ -ketoacyl-synthase, dehydrase, enoyl-ACP-reductase,  $\beta$ -ketoacyl-reductase, thioesterase and acyl carrier protein.

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<sub>3</sub>), 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.*<sup>1</sup> 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.*<sup>2</sup> established that tumours convert glucose or acetate into lipids at a rate similar to that observed in liver<sup>2</sup>. 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<sup>3</sup>. Several decades later, fatty acid synthase (FASN) was identified as the tumour antigen OA-519 in aggressive breast cancer<sup>4</sup>. Numerous studies have since confirmed the importance of FA biosynthesis for cancer cell growth and survival<sup>5,6</sup> (FIG. 1).

The modular nature of lipids, particularly those containing several FAs, determines the enormous structural complexity in this class of molecules<sup>7</sup>. 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<sup>8</sup>. Expression of FASN is also found in proliferating fetal tissues<sup>9</sup>, 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<sup>10</sup> 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

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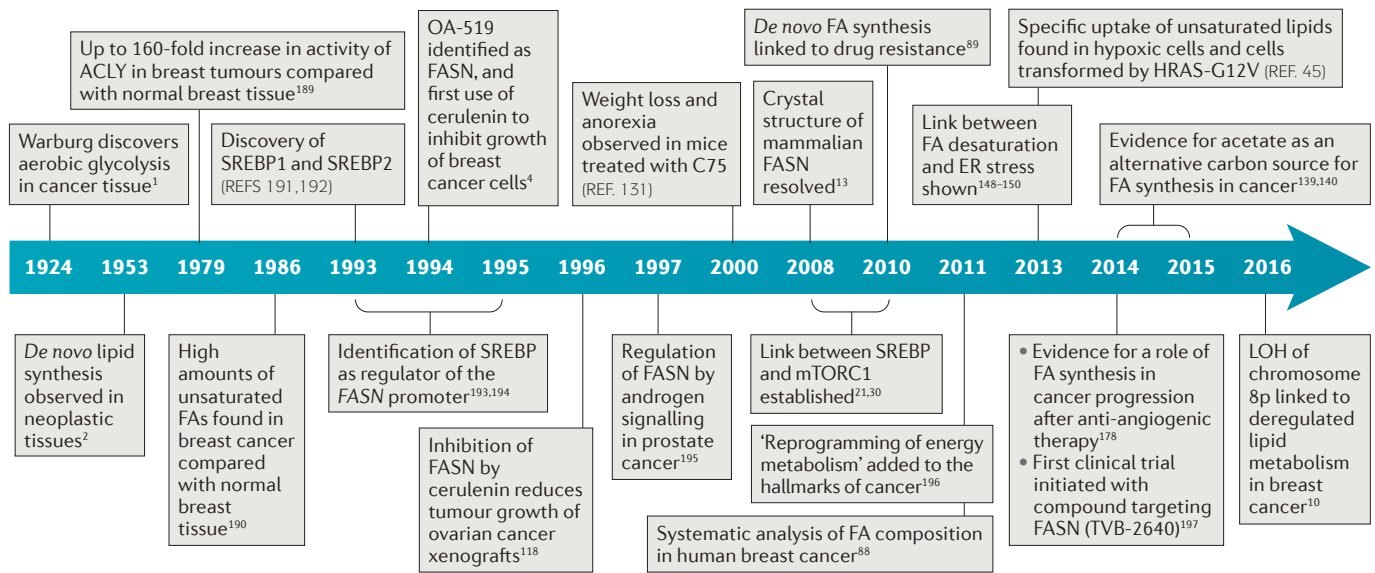


Figure 1 | **Fatty acid synthesis in cancer.** Major events demonstrating the importance of fatty acid (FA) synthesis in cancer cells. ACLY, ATP-citrate lyase; ER, endoplasmic reticulum; FASN, fatty acid synthase; LOH, loss of heterozygosity; mTORC1, mTOR complex 1; SREBP, sterol regulatory element binding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

mechanisms. Under normoxic conditions, normal cells use mainly pyruvate, the product of glycolysis, to feed the mitochondrial tricarboxylic acid (TCA) cycle<sup>6</sup>. This process generates citrate, which is cleaved into acetyl-CoA and oxaloacetate by ATP-citrate lyase (ACLY) in the cytoplasm<sup>11</sup>. Malonyl-CoA is then formed by acetyl-CoA carboxylases (ACCs, also known as ACACs), enzymes that are highly regulated by phosphorylation and allosteric regulation<sup>12</sup>. 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  $\beta$ -oxidation (BOX 1). The serial condensation of seven malonyl-CoA molecules and one priming acetyl-CoA by the multifunctional enzyme FASN<sup>13</sup> 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<sup>14,15</sup>. 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<sup>17</sup>. These target genes also encode enzymes of the cholesterol biosynthesis pathway, discussed in greater detail by Mullen *et al.*<sup>18</sup> 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.

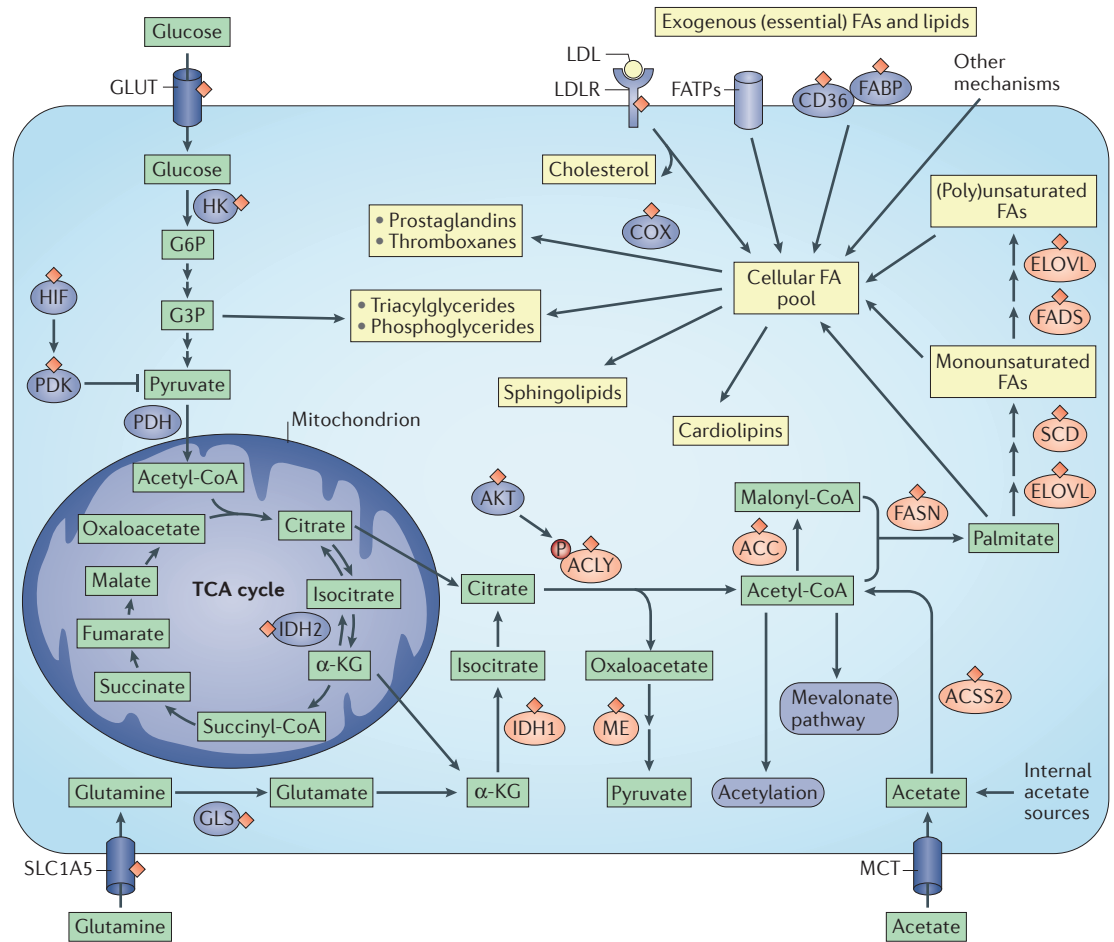
FA synthesis requires large amounts of NADPH, an essential cofactor for biosynthetic reactions. SREBP also regulates several processes involved in the regeneration of NADPH, including enzymes of the oxidative pentose phosphate pathway, malic enzymes (ME1 and ME2) and isocitrate dehydrogenases (IDH1, IDH2 and IDH3)<sup>19-21</sup>. SREBP1 has also been connected to the one-carbon cycle<sup>22</sup>, 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<sup>23</sup>. Their activation requires proteolytic processing by Golgi-resident proteases (membrane-bound transcription factor site 1 protease (MBTSP1) and MBTSP2). The canonical pathways for the regulation of SREBP involve binding to the SREBP cleavage-activating protein (SCAP)<sup>24</sup>. 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<sup>25</sup> (FIG. 3a). A second mechanism regulating SREBP processing is dependent on PC. Decreased PC levels in the Golgi membrane cause the translocation of MBTSPs 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<sup>26</sup>, 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<sup>27–29</sup>. 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<sup>30</sup>. SREBP target genes were also found to be a major component of the transcriptional response to mTORC1 activation<sup>21</sup>, 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- $\gamma$  co-activator 1 $\alpha$



**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  $\Delta 9$  position by stearoyl-CoA desaturases (SCDs). Other FA desaturases (FADSs) can introduce double bonds at the  $\Delta 5$  or  $\Delta 6$  position, or at  $\Delta 9$  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.  $\alpha$ -KG,  $\alpha$ -ketoglutarate; ACC, acetyl-CoA carboxylase; ACS2, 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.

**$\beta$ -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 |  $\beta$ -Oxidation

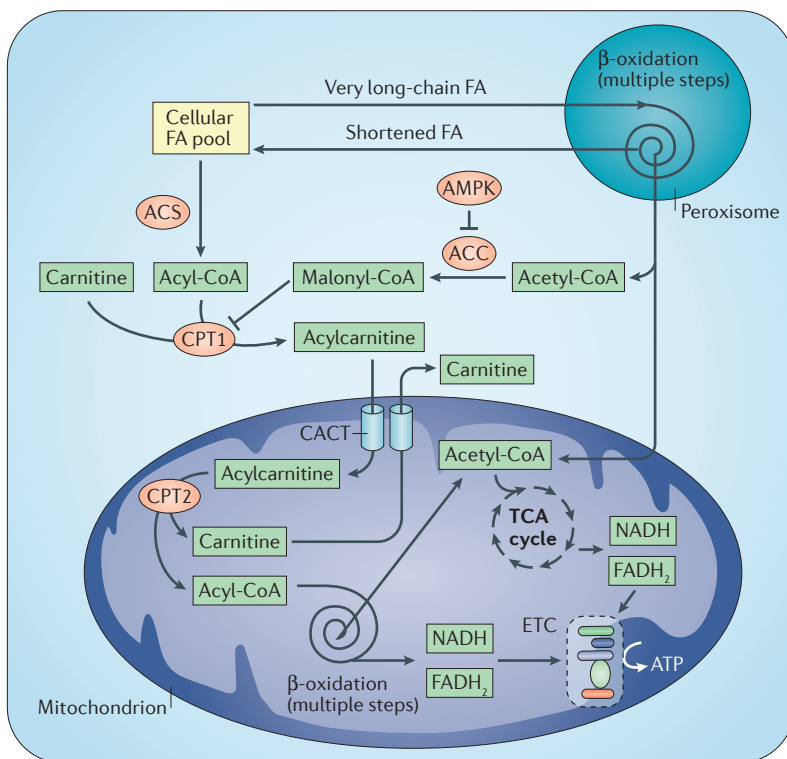
Fatty acids (FAs) are energy-rich compounds and their oxidation produces about twice the energy compared with carbohydrates (39 KJ g<sup>-1</sup> for palmitate compared with 15 KJ g<sup>-1</sup> for glucose (PubChem Compound Database)). FAs are also the preferred substrates for energy storage, mainly 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<sup>182</sup>.

Generating energy from stored TAGs requires initial cleavage of acyl chains from the glycerol backbone through a process called lipolysis<sup>183</sup>. 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<sup>184</sup>.

$\beta$ -Oxidation generates energy at several steps: the step-wise shortening of acyl-CoA generates one molecule of FADH<sub>2</sub> and NADH for every 2-carbon unit released. Each acetyl-CoA molecule then yields 3 molecules of NADH, 1 molecule of FADH<sub>2</sub> 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)<sup>185</sup> reduces malonyl-CoA levels and enables the activation of  $\beta$ -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  $\beta$ -oxidation in cancer. However, several reports have demonstrated that cancer cells require  $\beta$ -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<sup>187</sup>. More recently, it was shown that  $\beta$ -oxidation is an important bioenergetics pathway in triple-negative breast cancer and is required for the activation of SRC<sup>188</sup>. 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.

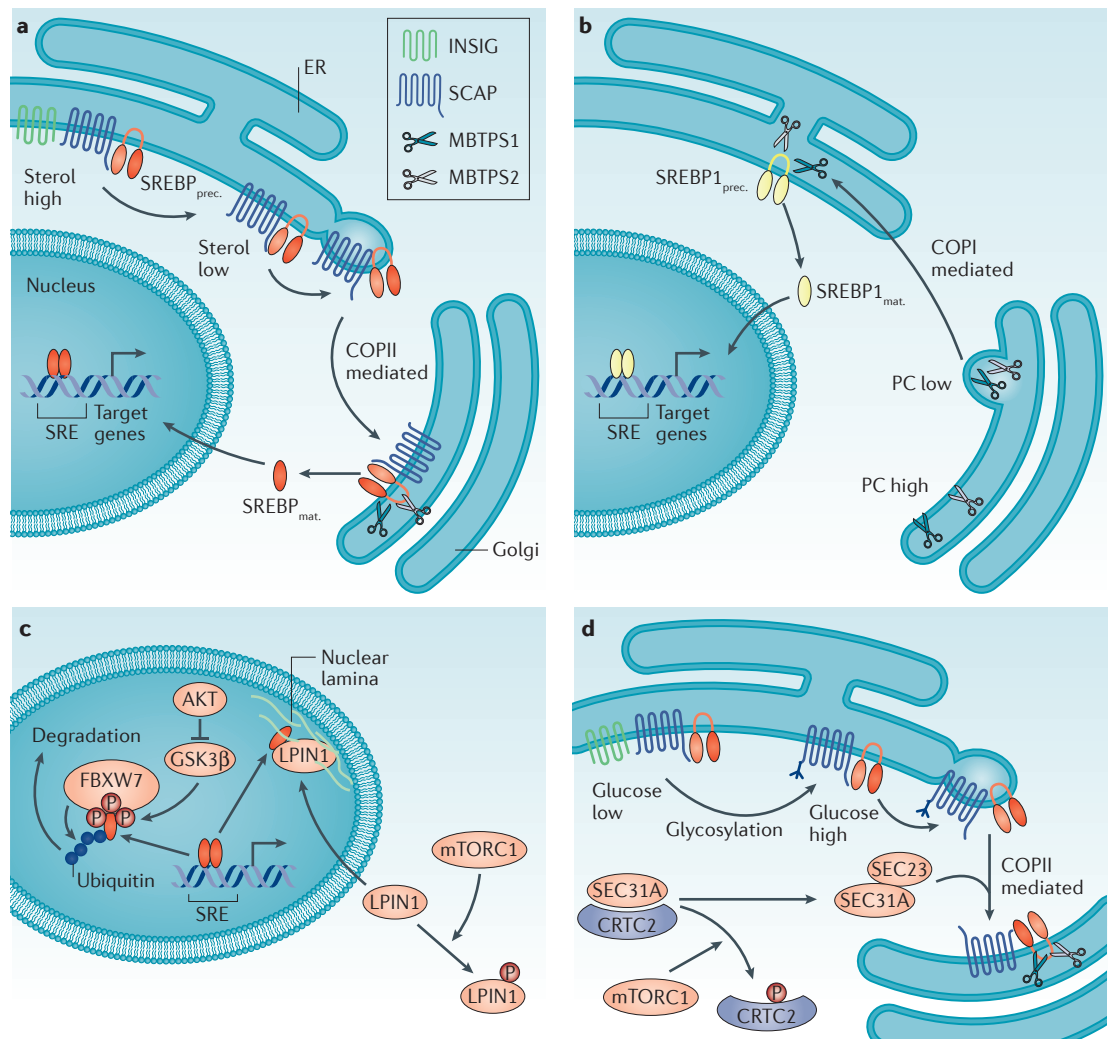
(PPARGC1A; also known as PGC1A)<sup>31</sup>. LPIN1 also binds to mature SREBPs, resulting in their sequestration to the nuclear lamina, thus preventing their access to active promoters<sup>32</sup> (FIG. 3c). Phosphorylation by mTORC1 prevents nuclear translocation of LPIN1 and restores SREBP activity<sup>32</sup>. 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<sup>33</sup>. 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<sup>FBXW7</sup> E3-ubiquitin ligase complex, which is frequently mutated or deleted in human cancer<sup>34</sup>. FBXW7 binding to SREBP requires phosphorylation of SREBP by glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ )<sup>35,36</sup>. As GSK3 $\beta$  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)<sup>37</sup>. It has been shown that ChREBP is activated in cancer cells in response to mitogenic signals to promote anabolic metabolism, including enhanced lipid biosynthesis<sup>38</sup>. Moreover, MondoA is induced by the proto-oncogene MYC to drive glutaminolysis and lipogenesis in cancer cells<sup>39</sup>. Interestingly, the synthetic lethality of blocking MondoA in cancer cells with high levels of MYC activity could be fully prevented by supplementation with mono-unsaturated FAs<sup>39</sup>, 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<sub>prec.</sub>) 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<sub>mat.</sub>), 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<sup>4</sup>. 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<sup>41</sup>. 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<sup>42,43</sup>, and the direct synthesis of acetyl-CoA from acetate by cytoplasmic acetyl-CoA synthetase (ACSS2)<sup>44</sup>.

**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<sup>45</sup>. 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)<sup>46</sup>. Upon re-oxygenation, cells used these stored lipids for energy production and antioxidant defence<sup>46</sup>. 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<sup>47,48</sup>.

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<sup>45</sup>. 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<sup>49</sup> (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,  $\alpha$ -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<sup>50</sup>. 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<sup>50</sup>. 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  $\Delta 9$  position of palmitoyl-CoA and stearoyl-CoA to generate monounsaturated FAs. As this reaction requires O<sub>2</sub>, the synthesis of monounsaturated FAs is compromised under severe hypoxia<sup>45</sup>. However, expression of SCD was induced in response to intermittent hypoxia in mice<sup>51</sup> and after exposure to lipid- and oxygen-deprived conditions in glioblastoma cells<sup>52</sup>, suggesting that reduced availability of oxygen for FA desaturation could at least partially be compensated by increasing SCD levels. In addition, roles for the  $\Delta 5$  FA desaturase FADS1 and the  $\Delta 6$  FA desaturase FADS2 are also emerging<sup>53</sup>. These enzymes are involved in the generation of polyunsaturated FAs (PUFAs), which are important modulators of inflammation and immune responses<sup>54</sup>.

**Metabolic symbiosis**

It is well established that systemic mobilization of lipids from adipose tissue fuels tumour growth during cancer cachexia<sup>55</sup>. 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<sup>56</sup>. 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  $\beta$ -oxidation<sup>58</sup> (BOX 1). Moreover, leukaemia stem cells evade chemotherapy by migrating to gonadal fat tissue, where they use adipose-derived

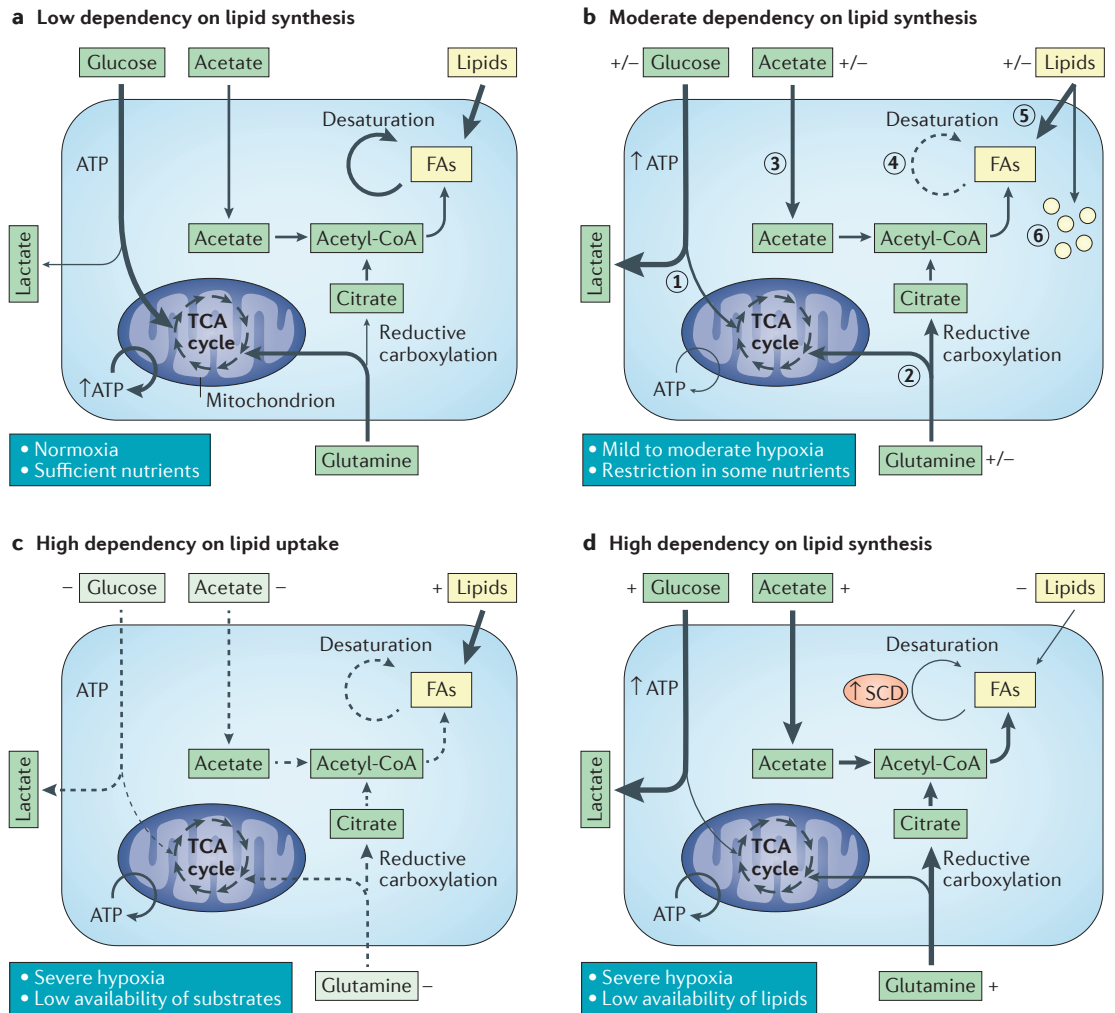


Figure 4 | **Metabolic flexibility in the tumour microenvironment.** **a** | Cancer cells near a functional blood vessel have sufficient nutrients and oxygen. They may use *de novo* lipid synthesis to convert blood-derived nutrients into fatty acids (FAs) to support rapid cell growth and proliferation. 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 stearyl-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<sup>59</sup>. 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<sup>60</sup>.

**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<sup>61</sup>. 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*<sup>30</sup>. 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<sup>62</sup>. The four acyl chains in CLs undergo constant remodelling through the action of phospholipases and acyltransferases<sup>63</sup>, 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*<sup>62</sup>, 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<sup>64</sup>.

In contrast to the original Warburg hypothesis<sup>65</sup>, many cancers maintain active mitochondria and flux through the ETC<sup>66</sup>. 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<sup>67</sup>. 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<sup>68,69</sup>. Interestingly, inhibition of FA desaturation also increased the sensitivity of cancer cells to chemotherapeutic agents that induce apoptosis via the mitochondrial pathway<sup>68,69</sup>, 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<sup>70</sup>. WNT proteins are modified by esterification of a palmitoleoyl chain through the activity of the membrane-bound O-acyltransferase porcupine (PORCN)<sup>71</sup>. Interestingly, inhibition of PORCN was effective in blocking growth of cancers that depend on excess production and secretion of WNT<sup>72,73</sup>. The preference for  $\Delta 9$ -desaturated acyl chains for WNT acylation implies functional consequences of this modification and explains why SCD is crucial for the activity of the WNT- $\beta$ -catenin pathway<sup>74</sup>. In addition, unsaturated FAs also regulate  $\beta$ -catenin stability independently of WNT by promoting the polymerization of FAS-associated factor 1 (FAF1), which mediates the interaction between  $\beta$ -catenin and the proteasome<sup>75</sup>. As aberrant activation of the WNT- $\beta$ -catenin pathway promotes the loss of cell-cell adhesion and disrupts epithelial cell polarity<sup>76</sup>, 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<sup>77</sup>.

**Lipid mediators.** Lipids can also function as important signalling molecules. These include the biologically active lipids sphingosine-1-phosphate (S1P)<sup>78</sup> and lysophosphatidic acid (LPA)<sup>79</sup>, which control inflammation, cell migration and survival in cancer, and the lipid second messengers DAG<sup>80</sup>, inositol-1,4,5-trisphosphate (IP<sub>3</sub>; also known as Ins(1,4,5)P<sub>3</sub>) and PIP<sub>3</sub> (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<sup>79</sup>. Interestingly, melanoma cells break down LPA to produce a local gradient that drives their dispersal<sup>82</sup>. 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<sup>83</sup>. 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<sup>84</sup> and that unsaturated LPA species selectively induce migration of immature dendritic cells in mice<sup>85</sup>. 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<sup>86</sup>, 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

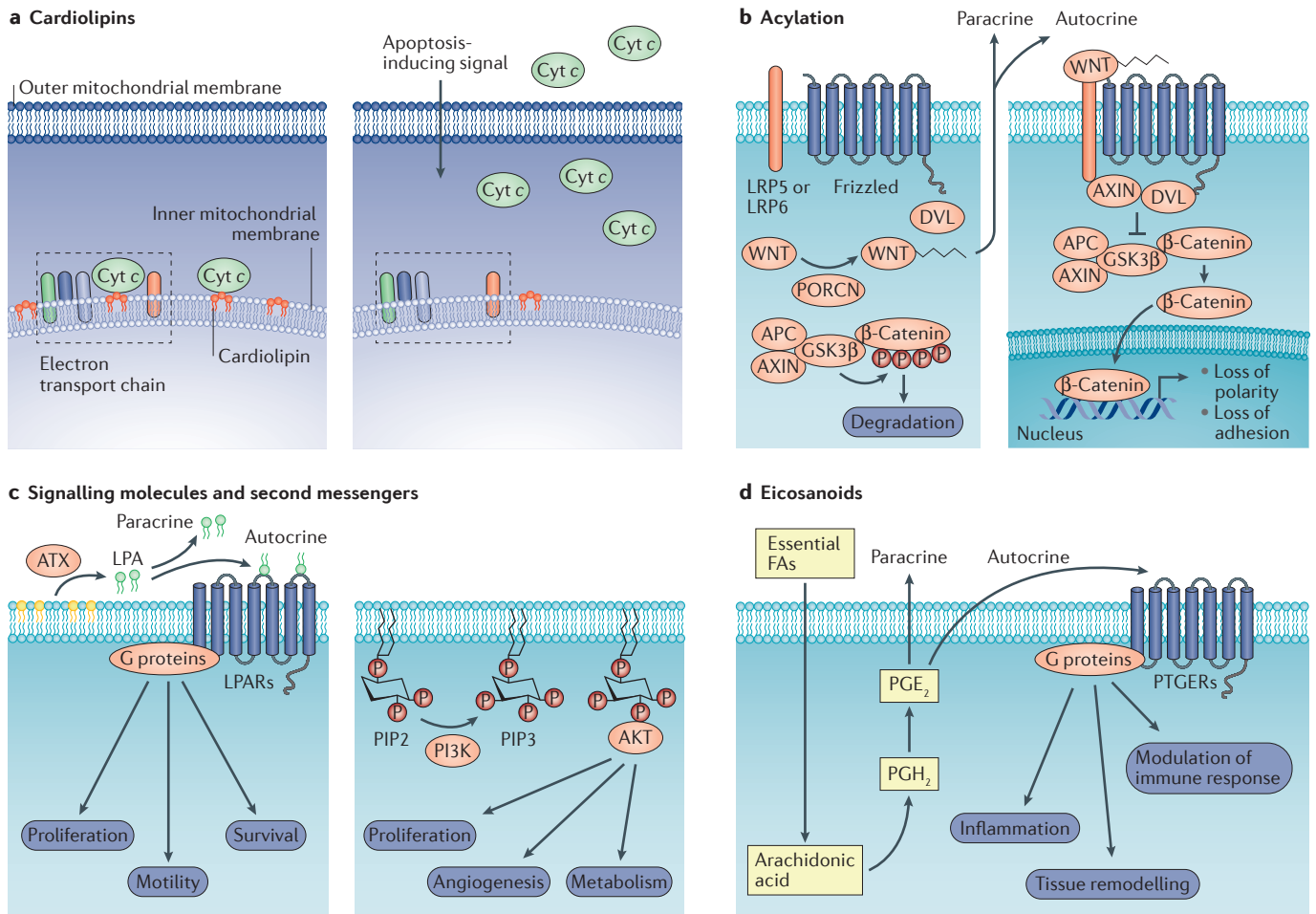
**Acylation**

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  $\beta$ -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– $\beta$ -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 (PIP<sub>3</sub>; also known as PtdIns(3,4,5)P<sub>3</sub>) activates AKT. **d** | Arachidonic acid is the substrate for the synthesis of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), which binds to prostaglandin E receptors (PTGERs) to regulate inflammation and immune response. APC, adenomatous polyposis coli; DVL, Dishevelled; GSK3 $\beta$ , glycogen synthase kinase 3 $\beta$ ; LRP, low-density lipoprotein receptor-related protein; PGH<sub>2</sub>, prostaglandin H<sub>2</sub>; PIP<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate (also known as PtdIns(4,5)P<sub>2</sub>); PORCN, membrane-bound O-acyltransferase porcupine.

aggressive cancer cells rely more heavily on exogenous FAs for the synthesis of signalling lipids<sup>87</sup>. 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<sup>88</sup>. This higher saturation level protects cancer cells from ROS, as saturated membrane lipids are less susceptible to peroxidation<sup>89</sup>.

However, lipid peroxides also contribute to cellular signalling as intermediates in the synthesis of eicosanoids<sup>54</sup>. 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<sup>90</sup>.

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<sup>90</sup>. 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<sup>91–93</sup>. One of the direct effects of prostaglandins, specifically prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), on tumour cells is the induction of proliferation via activation of the RAS–ERK<sup>94</sup> and the β-catenin pathways in colorectal cancer<sup>95</sup>. PGE<sub>2</sub> also suppresses the activation of anticancer immune pathways but induces tumour-promoting inflammation<sup>96</sup>. 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.

**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)<sup>97</sup>.

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<sub>2</sub> signalling<sup>98</sup>. Another study showed that in lung cancer cells, TGFβ signalling inhibits ChREBP leading to reduced *de novo* FA synthesis<sup>99</sup>. In these cells, knock-down of FASN reduced the expression of E-cadherin and increased cell migration and metastasis in a tail vein injection model in mice<sup>99</sup>.

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<sup>100</sup>. 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<sup>101</sup>, 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<sup>102</sup>. 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*<sup>102</sup>, suggesting that monounsaturated FAs promote this crucial step during tumour progression.

**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<sub>3</sub>) and lysophosphatidic acid (LPA))

**Tumour progression and drug resistance**

**Migration**

- Biophysical properties of structural lipids alter membrane fluidity
- Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) production by transforming growth factor-β induces epithelial-to-mesenchymal transition
- Small GTPases are prenylated via the mevalonate pathway

**Angiogenesis**

- PGE<sub>2</sub> 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<sub>2</sub> induces reprogramming of macrophages to the M2 subtype
- Release of PGE<sub>2</sub> 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

**Angiogenesis.** Metastatic dissemination, as well as primary and metastatic tumour growth, also depends on the induction of angiogenesis<sup>103</sup>. Signalling lipids, including PGE<sub>2</sub>, LPA and S1P, have important roles in stimulating vessel outgrowth and recruiting immune cells, particularly macrophages, which promote tumour angiogenesis<sup>104,105</sup>. Endothelial cells selectively use FA degradation not for energy generation, but to generate substrates for nucleotide biosynthesis<sup>106</sup>. Moreover, uptake of exogenous FAs by prostate cancer cells enhances the expression of vascular endothelial growth factor (VEGF) through a mechanism requiring FAPB5 and PPAR $\gamma$  (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<sup>108</sup>, such as PGE<sub>2</sub>. In cancer cells, PGE<sub>2</sub> generally dampens the immune response, for example, by inducing the release of the immunosuppressive cytokine interleukin-10 (IL-10)<sup>109</sup>. PGE<sub>2</sub> released by cancer cells can also shift tumour-associated macrophages from the tumour-inhibitory M1 to the tumour-promoting M2 phenotype<sup>110</sup>. Moreover, the release of PGE<sub>2</sub> 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)<sup>96</sup>.

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<sup>111</sup>. 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<sup>112</sup>. 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<sup>113</sup>. In addition, breast tumours can release free FAs to block the anti-tumour activity of cytotoxic T cells<sup>114</sup>. Moreover, secretion of linoleic acid by hepatocytes in non-alcoholic fatty liver disease (NAFLD) induces the selective loss of intrahepatic CD4<sup>+</sup> T cells and promotes the development of hepatocellular carcinoma<sup>115</sup>. 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 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  $\beta$ -ketoacyl-reductase activity of FASN and both inhibits proliferation and induces apoptosis in cancer cells *in vitro* and *in vivo*<sup>4,118–120</sup>. Similarly, the synthetic compound C75 blocked DNA replication<sup>121</sup>, caused apoptosis in several cancer cell lines<sup>119,122–124</sup> and was antitumorigenic in xenograft models of mesothelioma<sup>125</sup> as well as breast<sup>119</sup>, renal<sup>126</sup>, lung<sup>127</sup> and prostate cancer<sup>128</sup>. C75 also prevented breast cancer development in *HER2* (also known as *ERBB2*)-transgenic mice<sup>129</sup> and increased taxol sensitivity of breast cancer cells *in vitro*<sup>124</sup>. 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<sup>130</sup>.

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<sup>131</sup> and by inducing the expression of hypothalamic neuropeptides, which regulate energy intake and expenditure<sup>132</sup>. 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  $\beta$ -oxidation and excessive energy expenditure, thereby exacerbating the detrimental effect of this drug<sup>133</sup>. 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<sup>134</sup>. 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<sup>135</sup>, 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 1 | Fatty acid synthesis inhibitors in preclinical and clinical development

Compound	Mechanism of action	Preclinical model or clinical trial	Effect	Refs
<b>FASN</b>				
TVB-2640	NA	Refractory solid tumours, phase I	Ongoing trial	197
TVB-3166	Inhibition of the $\beta$ -ketoacyl-reductase activity	Multiple cancer cell lines, pancreatic cancer xenografts	Inhibition of proliferation and reduction in tumour growth	40,198
GSK2194069	Inhibition of the $\beta$ -ketoacyl-reductase activity	Prostate cancer xenografts	Reduction of tumour volume and reduction of acetate uptake	199
C93	Inhibition of the $\beta$ -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	<i>HER2</i> 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 $\beta$ -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
		<i>HER2</i> transgenic mice	Chemoprevention and increased taxol sensitivity	129
		Intracerebroventricular treatment in mice	Anorexia	195
Cerulenin	Irreversible inhibition of $\beta$ -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 <i>HER2</i> 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	
<b>Other targets</b>				
TOFA	Inhibition of ACCs	Lung, colon and breast cancer cell lines	Induction of apoptosis	119,144
Sorafenin 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 <i>TCL1</i> 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
<i>Other targets (cont.)</i>				
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<sup>99</sup>, 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<sup>6</sup>. For example, depletion or inhibition of ACLY efficiently blocked cancer cell growth and tumour formation<sup>61,136,137</sup>. 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<sup>138</sup>. Similarly, ACSS2-mediated production of acetyl-CoA from acetate contributes to FA biosynthesis in hypoxic cancer cells<sup>45,139</sup> 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<sup>139–141</sup>. Interestingly, acetate was also shown to be a major bioenergetic substrate for tumours in patients with glioblastoma or brain metastases of other cancer types<sup>142</sup>. 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<sup>143</sup>.

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<sup>119</sup>, an efficient inhibitor of  $\beta$ -oxidation (see BOX 1), inhibition of ACCs would block FA synthesis but simultaneously induce  $\beta$ -oxidation, resulting in more severe lipid depletion. Targeting of ACCs

by chemical inhibition<sup>144</sup> or silencing limits cancer cell proliferation<sup>145,146</sup>. However, silencing of *ACCI* or *ACC2* reduced oxidative stress in cancer cells and promoted xenograft growth<sup>147</sup>, 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<sup>148,149</sup>. This results in mitochondrial dysfunction and oxidative stress, leading to ER stress and induction of the unfolded protein response (UPR) pathway<sup>148,149</sup>. Interestingly, expression of myristoylated AKT in immortalized human epithelial cells increased their sensitivity towards SREBP silencing<sup>148</sup>, 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<sup>150</sup>. The connection between mTORC1 and SREBP and the control of ER homeostasis during proliferation and cell growth was also confirmed in *D. melanogaster* cells<sup>151</sup>. 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)<sup>152</sup>. 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<sup>152</sup>. 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<sup>153</sup>. 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<sup>148,149</sup>. 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<sup>52</sup>.

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, LXR $\alpha$  and LXR $\beta$  (also known as NR1H3 and NR1H2, respectively), which form heterodimers with the retinoid X receptor- $\alpha$  (RXR $\alpha$ ) 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<sup>154</sup>. 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<sup>156</sup>. 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<sup>157</sup>.

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<sup>158</sup>, has been shown to reduce the growth of prostate cancer xenografts<sup>159,160</sup>. The other is the natural compound betulin, which improved diet-induced obesity in mice by inhibiting SREBP activation<sup>161</sup>. Although betulin has shown antiproliferative effects on cancer cell lines<sup>162</sup>, 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<sup>163</sup>. Specific strategies, such as the recent advance of phthalimide conjugates, which selectively induce the degradation of target proteins<sup>164</sup>, 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<sup>165</sup>. Moreover, inhibition of the desaturase SCD efficiently blocked cancer cell proliferation by selectively depleting monounsaturated FAs<sup>69,166–169</sup>. This inhibited oncogenic signalling pathways<sup>170</sup>, activated AMP-activated protein kinase (AMPK)<sup>168</sup> and increased sensitivity towards chemotherapies<sup>68,69</sup>. 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<sup>171</sup>, gastric<sup>169</sup> and liver cancer<sup>172</sup> and prevented orthotopic growth of prostate cancer cells *in vivo*<sup>69</sup>, 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<sup>173</sup>. Alterations in lipid metabolism can affect drug resistance. Several studies have demonstrated that inhibition of FASN increases the chemosensitivity of breast cancer cells<sup>174–176</sup>. As already described above, inhibition of FA desaturation increases the sensitivity of cancer cells towards apoptosis-inducing drugs by changing CL synthesis<sup>68,69</sup>. 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<sup>177</sup>. A potential role of lipid metabolism in this process was recently reported in tumours following the withdrawal of the angiogenesis inhibitor sunitinib<sup>178</sup>. 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<sup>178</sup>. 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<sup>179</sup>. 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<sup>69,139</sup>. 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-<sup>11</sup>C]acetate demonstrated FA biosynthesis in lung tumours induced by oncogenic KRAS (KRAS-G12D) in mice<sup>180</sup>. It would be interesting to conduct similar experiments using derivatives of palmitate, primarily used to analyse myocardial metabolism<sup>181</sup>. 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.

- Warburg, O., Posener, K. & Negelein, E. Über den Stoffwechsel der Carcinomzelle. *Biochem. Zeitschr.* **152**, 309–344 (in German) (1924).
- Medes, G., Thomas, A. & Weinhouse, S. Metabolism of neoplastic tissue. IV. 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 tissues.**
- Ookhtens, M., Kannan, R., Lyon, I. & Baker, N. Liver and adipose tissue contributions to newly formed fatty acids in an ascites tumor. *Am. J. Physiol.* **247**, R146–R153 (1984).
- Kuhajda, F. P. *et al.* Fatty acid synthesis: a potential selective target for antineoplastic therapy. *Proc. Natl Acad. Sci. USA* **91**, 6379–6383 (1994).
- Santos, C. R. & Schulze, A. Lipid metabolism in cancer. *FEBS J.* **279**, 2610–2623 (2012).
- Currie, E., Schulze, A., Zechner, R., Walther, T. C. & Farese, R. V. Jr. Cellular fatty acid metabolism and cancer. *Cell Metab.* **18**, 153–161 (2013).
- Shevchenko, A. & Simons, K. Lipidomics: coming to grips with lipid diversity. *Nat. Rev. Mol. Cell Biol.* **11**, 593–598 (2010).
- Menendez, J. A. & Lupu, R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat. Rev. Cancer* **7**, 763–777 (2007).
- Kusakabe, T. *et al.* Fatty acid synthase is expressed mainly in adult hormone-sensitive cells or cells with high lipid metabolism and in proliferating fetal cells. *J. Histochem. Cytochem.* **48**, 613–622 (2000).
- Cai, Y. *et al.* Loss of chromosome 8p governs tumor progression and drug response by altering lipid metabolism. *Cancer Cell* **29**, 751–766 (2016).
- Zaidi, N., Swinnen, J. V. & Smans, K. ATP-citrate lyase: a key player in cancer metabolism. *Cancer Res.* **72**, 3709–3714 (2012).
- Brownsey, R. W., Boone, A. N., Elliott, J. E., Kulpa, J. E. & Lee, W. M. Regulation of acetyl-CoA carboxylase. *Biochem. Soc. Trans.* **34**, 223–227 (2006).
- Maier, T., Leibundgut, M. & Ban, N. The crystal structure of a mammalian fatty acid synthase. *Science* **321**, 1315–1322 (2008).
- Jakobsson, A., Westerberg, R. & Jacobsson, A. Fatty acid elongases in mammals: their regulation and roles in metabolism. *Prog. Lipid Res.* **45**, 237–249 (2006).
- Igal, R. A. Stearoyl-CoA desaturase-1: a novel key player in the mechanisms of cell proliferation, programmed cell death and transformation to cancer. *Carcinogenesis* **31**, 1509–1515 (2010).
- Horton, J. D. Sterol regulatory element-binding proteins: transcriptional activators of lipid synthesis. *Biochem. Soc. Trans.* **30**, 1091–1095 (2002).
- Amemiya-Kudo, M. *et al.* Transcriptional activities of nuclear SREBP-1a, -1c, and -2 to different target promoters of lipogenic and cholesterologenic genes. *J. Lipid Res.* **43**, 1220–1235 (2002).
- Mullen, P. J., Yu, R., Longo, J., Archer, M. C. & Penn, L. Z. The interplay between cell signaling and the mevalonate pathway in cancer. *Nat. Rev. Cancer* <https://dx.doi.org/10.1038/nrc.2016.76> (2016).
- Shimano, H. *et al.* Sterol regulatory element-binding protein-1 as a key transcription factor for nutritional induction of lipogenic enzyme genes. *J. Biol. Chem.* **274**, 35832–35839 (1999).
- Shechter, I., Dai, P., Huo, L. & Guan, G. *IDH1* gene transcription is sterol regulated and activated by SREBP-1a and SREBP-2 in human hepatoma HepG2 cells: evidence that *IDH1* may regulate lipogenesis in hepatic cells. *J. Lipid Res.* **44**, 2169–2180 (2003).
- Duvel, K. *et al.* Activation of a metabolic gene regulatory network downstream of mTOR complex 1. *Mol. Cell* **39**, 171–183 (2010).  
**This study identified SREBP as a major component of the gene regulatory network downstream of mTORC1.**
- Walker, A. K. *et al.* A conserved SREBP-1/Phosphatidylcholine feedback circuit regulates lipogenesis in metazoans. *Cell* **147**, 840–852 (2011).
- Nohturfft, A. & Zhang, S. C. Coordination of lipid metabolism in membrane biogenesis. *Annu. Rev. Cell Dev. Biol.* **25**, 539–566 (2009).
- Brown, M. S. & Goldstein, J. L. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. *Cell* **89**, 331–340 (1997).
- Espenshade, P. J. & Hughes, A. L. Regulation of sterol synthesis in eukaryotes. *Annu. Rev. Genet.* **41**, 401–427 (2007).
- Horton, J. D., Goldstein, J. L. & Brown, M. S. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J. Clin. Invest.* **109**, 1125–1131 (2002).
- Fleischmann, M. & Iynedjian, P. B. Regulation of sterol regulatory-element binding protein 1 gene expression in liver: role of insulin and protein kinase B/Akt. *Biochem. J.* **349**, 13–17 (2000).
- Yang, Y. A., Han, W. F., Morin, P. J., Chrest, F. J. & Pizer, E. S. Activation of fatty acid synthesis during neoplastic transformation: role of mitogen-activated protein kinase and phosphatidylinositol 3-kinase. *Exp. Cell Res.* **279**, 80–90 (2002).
- Porstmann, T. *et al.* PKB/Akt induces transcription of enzymes involved in cholesterol and fatty acid biosynthesis via activation of SREBP. *Oncogene* **24**, 6465–6481 (2005).
- Porstmann, T. *et al.* SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth. *Cell Metab.* **8**, 224–236 (2008).  
**This study was the first to demonstrate that SREBP is regulated by mTORC1 and contributes to cell growth.**
- Finck, B. N. *et al.* Lipin 1 is an inducible amplifier of the hepatic PGC-1 $\alpha$ /PPAR $\alpha$  regulatory pathway. *Cell Metab.* **4**, 199–210 (2006).
- Peterson, T. R. *et al.* mTOR complex 1 regulates lipin 1 localization to control the SREBP pathway. *Cell* **146**, 408–420 (2011).  
**This study implicated LPIN1 in the regulation of SREBP by mTORC1.**
- Han, J. *et al.* The CREB coactivator CRTC2 controls hepatic lipid metabolism by regulating SREBP1. *Nature* **524**, 243–246 (2015).  
**This study showed regulation of SREBP1 processing by mTORC1 through phosphorylation of CRTC2.**
- Welcker, M. & Clurman, B. E. FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. *Nat. Rev. Cancer* **8**, 83–93 (2008).
- Sundqvist, A. *et al.* Control of lipid metabolism by phosphorylation-dependent degradation of the SREBP family of transcription factors by SCF(Fbw7). *Cell Metab.* **1**, 379–391 (2005).
- Bengochea-Alonso, M. T. & Ericsson, 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 $\beta$ -dependent phosphorylation and ubiquitination by the FBXW7 ubiquitin ligase.**
- Dang, C. V. MYC on the path to cancer. *Cell* **149**, 22–35 (2012).
- Tong, X., Zhao, F., Mancuso, A., Gruber, J. J. & Thompson, C. B. The glucose-responsive transcription factor ChREBP contributes to glucose-dependent anabolic synthesis and cell proliferation. *Proc. Natl Acad. Sci. USA* **106**, 21660–21665 (2009).

39. Carroll, P. A. *et al.* Deregulated myc requires MondoA/Mlx for metabolic reprogramming and tumorigenesis. *Cancer Cell* **27**, 271–285 (2015). **This study demonstrated that induction of lipid synthesis by MondoA is essential for MYC transformed cells. The effect of MondoA repression was rescued by oleic acid, confirming the importance of monounsaturated FAs for cancer cells.**
40. Ventura, R. *et al.* Inhibition of *de novo* palmitate synthesis by fatty acid synthase induces apoptosis in tumor cells by remodeling cell membranes, inhibiting signaling pathways, and reprogramming gene expression. *EBioMedicine* **2**, 806–822 (2015).
41. Papandreou, I., Cairns, R. A., Fontana, L., Lim, A. L. & Denko, N. C. HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. *Cell Metab.* **3**, 187–197 (2006).
42. Wise, D. R. *et al.* Hypoxia promotes isocitrate dehydrogenase-dependent carboxylation of  $\alpha$ -ketoglutarate to citrate to support cell growth and viability. *Proc. Natl Acad. Sci. USA* **108**, 19611–19616 (2011).
43. Metallo, C. M. *et al.* Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. *Nature* **481**, 380–384 (2011).
44. Kamphorst, J. J., Chung, M. K., Fan, J. & Rabinowitz, J. D. Quantitative analysis of acetyl-CoA production in hypoxic cancer cells reveals substantial contribution from acetate. *Cancer Metab.* **2**, 23 (2014).
45. Kamphorst, J. J. *et al.* Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. *Proc. Natl Acad. Sci. USA* **110**, 8882–8887 (2013). **This study showed that hypoxic or KRAS-transformed cells selectively take up monounsaturated lipids.**
46. Bensaad, K. *et al.* Fatty acid uptake and lipid storage induced by HIF-1 $\alpha$  contribute to cell growth and survival after hypoxia-reoxygenation. *Cell Rep.* **9**, 349–365 (2014). **This study implicated lipid storage by hypoxic cells in energy provision after reoxygenation.**
47. Michiels, C., Tellier, C. & Feron, O. Cycling hypoxia: a key feature of the tumor microenvironment. *Biochim. Biophys. Acta* **1866**, 76–86 (2016).
48. Yasui, H. *et al.* Low-field magnetic resonance imaging to visualize chronic and cycling hypoxia in tumor-bearing mice. *Cancer Res.* **70**, 6427–6436 (2010).
49. Gatenby, R. A. & Gillies, R. J. Why do cancers have high aerobic glycolysis? *Nat. Rev. Cancer* **4**, 891–899 (2004).
50. Yue, S. *et al.* Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness. *Cell Metab.* **19**, 393–406 (2014). **This study connected cholesterol esterification to maintain SREBP activity with aggressive behaviour of prostate cancers.**
51. Li, J. *et al.* Altered metabolic responses to intermittent hypoxia in mice with partial deficiency of hypoxia-inducible factor-1 $\alpha$ . *Physiol. Genom.* **25**, 450–457 (2006).
52. Lewis, C. A. *et al.* SREBP maintains lipid biosynthesis and viability of cancer cells under lipid- and oxygen-deprived conditions and defines a gene signature associated with poor survival in glioblastoma multiforme. *Oncogene* **43**, 5128–5140 (2015).
53. Tosi, F., Sartori, F., Guarini, P., Olivieri, O. & Martinelli, N. Delta-5 and delta-6 desaturases: crucial enzymes in polyunsaturated fatty acid-related pathways with pleiotropic influences in health and disease. *Adv. Exp. Med. Biol.* **824**, 61–81 (2014).
54. Wymann, M. P. & Schneider, R. Lipid signalling in disease. *Nat. Rev. Mol. Cell Biol.* **9**, 162–176 (2008).
55. Argiles, J. M., Busquets, S., Stemmler, B. & Lopez-Soriano, F. J. Cancer cachexia: understanding the molecular basis. *Nat. Rev. Cancer* **14**, 754–762 (2014).
56. Sonveaux, P. *et al.* Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. *J. Clin. Invest.* **118**, 3930–3942 (2008).
57. Romero, I. L., Mukherjee, A., Kenny, H. A., Litchfield, L. M. & Lengyel, E. Molecular pathways: trafficking of metabolic resources in the tumor microenvironment. *Clin. Cancer Res.* **21**, 680–686 (2015).
58. Nieman, K. M. *et al.* Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nat. Med.* **17**, 1498–1503 (2011). **This study provided an elegant example of metabolic symbiosis of cancer cells and adipocytes.**
59. Ye, H. *et al.* Leukemic stem cells evade chemotherapy by metabolic adaptation to an adipose tissue niche. *Cell Stem Cell* **19**, 23–37 (2016).
60. Caiado, F., Silva-Santos, B. & Norell, H. Intra-tumour heterogeneity - going beyond genetics. *FEBS J.* **283**, 2245–2258 (2016).
61. Hatzivassiliou, G. *et al.* ATP citrate lyase inhibition can suppress tumor cell growth. *Cancer Cell* **8**, 311–321 (2005).
62. Schug, Z. T. & Gottlieb, E. Cardiolipin acts as a mitochondrial signalling platform to launch apoptosis. *Biochim. Biophys. Acta* **1788**, 2022–2031 (2009).
63. Chicco, A. J. & Sparagna, G. C. Role of cardiolipin alterations in mitochondrial dysfunction and disease. *Am. J. Physiol. Cell Physiol.* **292**, C33–44 (2007).
64. Kiebish, M. A., Han, X., Cheng, H., Chuang, J. H. & Seyfried, T. N. Cardiolipin and electron transport chain abnormalities in mouse brain tumor mitochondria: lipidomic evidence supporting the Warburg theory of cancer. *J. Lipid Res.* **49**, 2545–2556 (2008).
65. Warburg, O. On the origin of cancer cells. *Science* **123**, 309–314 (1956).
66. Wallace, D. C. Mitochondria and cancer. *Nat. Rev. Cancer* **12**, 685–698 (2012).
67. Mashima, T. *et al.* p53-defective tumors with a functional apoptosome-mediated pathway: a new therapeutic target. *J. Natl Cancer Inst.* **97**, 765–777 (2005).
68. Potze, L. *et al.* Betulinic acid induces a novel cell death pathway that depends on cardiolipin modification. *Oncogene* **35**, 427–437 (2015).
69. Peck, B. *et al.* Inhibition of fatty acid desaturation is detrimental to cancer cell survival in metabolically compromised environments. *Cancer Metab.* **4**, 6 (2016). **This study analysed the effect of SCD inhibition on lipid composition and survival in cancer cells. It also demonstrated that SCD silencing efficiently blocks growth of prostate cancer orthografts.**
70. Schepers, A. & Clevers, H. Wnt signaling, stem cells, and cancer of the gastrointestinal tract. *Cold Spring Harb. Perspect. Biol.* **4**, a007989 (2012).
71. Nile, A. H. & Hannouh, R. N. Fatty acylation of Wnt proteins. *Nat. Chem. Biol.* **12**, 60–69 (2016).
72. Proffitt, K. D. *et al.* Pharmacological inhibition of the Wnt acyltransferase PORCN prevents growth of WNT-driven mammary cancer. *Cancer Res.* **73**, 502–507 (2013).
73. Liu, J. *et al.* Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. *Proc. Natl Acad. Sci. USA* **110**, 20224–20229 (2013).
74. Rios-Esteves, J. & Resh, M. D. Stearoyl CoA desaturase is required to produce active, lipid-modified Wnt proteins. *Cell Rep.* **4**, 1072–1081 (2013).
75. Kim, H. *et al.* Unsaturated fatty acids stimulate tumor growth through stabilization of  $\beta$ -catenin. *Cell Rep.* **13**, 496–503 (2015).
76. Anastas, J. N. & Moon, R. T. WNT signalling pathways as therapeutic targets in cancer. *Nat. Rev. Cancer* **13**, 11–26 (2013).
77. Levental, I., Grzybek, M. & Simons, K. Greasing their way: lipid modifications determine protein association with membrane rafts. *Biochemistry* **49**, 6305–6316 (2010).
78. Pyne, N. J. & Pyne, S. Sphingosine 1-phosphate and cancer. *Nat. Rev. Cancer* **10**, 489–503 (2010).
79. Park, J. B. *et al.* Phospholipase signalling networks in cancer. *Nat. Rev. Cancer* **12**, 782–792 (2012).
80. Griner, E. M. & Kazanietz, M. G. Protein kinase C and other diacylglycerol effectors in cancer. *Nat. Rev. Cancer* **7**, 281–294 (2007).
81. Vanhaesebroeck, B., Stephens, L. & Hawkins, P. PI3K signalling: the path to discovery and understanding. *Nat. Rev. Mol. Cell Biol.* **13**, 195–203 (2012).
82. Muinonen-Martin, A. J. *et al.* Melanoma cells break down LPA to establish local gradients that drive chemotactic dispersal. *PLoS Biol.* **12**, e1001966 (2014).
83. Choi, J. W. *et al.* LPA receptors: subtypes and biological actions. *Annu. Rev. Pharmacol. Toxicol.* **50**, 157–186 (2010).
84. Bandoh, K. *et al.* Lysophosphatidic acid (LPA) receptors of the EDG family are differentially activated by LPA species. Structure-activity relationship of cloned LPA receptors. *FEBS Lett.* **478**, 159–165 (2000).
85. Chan, L. C. *et al.* LPA3 receptor mediates chemotaxis of immature murine dendritic cells to unsaturated lysophosphatidic acid (LPA). *J. Leukoc. Biol.* **82**, 1193–1200 (2007).
86. Goto, T. *et al.* The expression profile of phosphatidylinositol in high spatial resolution imaging mass spectrometry as a potential biomarker for prostate cancer. *PLoS ONE* **9**, e90242 (2014).
87. Louie, S. M., Roberts, L. S., Mulvihill, M. M., Luo, K. & Nomura, D. K. Cancer cells incorporate and remodel exogenous palmitate into structural and oncogenic signaling lipids. *Biochim. Biophys. Acta* **1831**, 1566–1572 (2013).
88. Hilvo, M. *et al.* Novel therapeutic opportunities offered by characterization of altered membrane lipid metabolism in breast cancer progression. *Cancer Res.* **71**, 3236–3245 (2011).
89. Rysman, E. *et al.* *De novo* lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. *Cancer Res.* **70**, 8117–8126 (2010).
90. Wang, D. & Dubois, R. N. Eicosanoids and cancer. *Nat. Rev. Cancer* **10**, 181–193 (2010).
91. Pan, Y. *et al.* Deletion of cyclooxygenase-2 inhibits Kras-induced lung carcinogenesis. *Oncotarget* **6**, 38816–38826 (2015).
92. Howe, L. R. *et al.* HER2/neu-induced mammary tumorigenesis and angiogenesis are reduced in cyclooxygenase-2 knockout mice. *Cancer Res.* **65**, 10113–10119 (2005).
93. Sonoshita, M. *et al.* Acceleration of intestinal polyposis through prostaglandin receptor EP2 in *Apc*<sup>d716</sup> knockout mice. *Nat. Med.* **7**, 1048–1051 (2001).
94. Wang, D., Buchanan, F. G., Wang, H., Dey, S. K. & DuBois, R. N. Prostaglandin E2 enhances intestinal adenoma growth via activation of the Ras/mitogen-activated protein kinase cascade. *Cancer Res.* **65**, 1822–1829 (2005).
95. Castellone, M. D., Teramoto, H., Williams, B. O., Druey, K. M. & Gutkind, J. S. Prostaglandin E2 promotes colon cancer cell growth through a G $\alpha$ -axin- $\beta$ -catenin signaling axis. *Science* **310**, 1504–1510 (2005).
96. Zelenay, S. *et al.* Cyclooxygenase-dependent tumor growth through evasion of immunity. *Cell* **162**, 1257–1270 (2015). **This study demonstrated the role of prostaglandin synthesis in the suppression of myeloid cell activation and immune evasion in melanoma.**
97. De Craene, B. & Berx, G. Regulatory networks defining EMT during cancer initiation and progression. *Nat. Rev. Cancer* **13**, 97–110 (2013).
98. Vo, B. T. *et al.* TGF- $\beta$  effects on prostate cancer cell migration and invasion are mediated by PGE2 through activation of PI3K/AKT/mTOR pathway. *Endocrinology* **154**, 1768–1779 (2013).
99. Jiang, L. *et al.* Metabolic reprogramming during TGF $\beta$ 1-induced epithelial-to-mesenchymal transition. *Oncogene* **34**, 3908–3916 (2015).
100. Nath, A., Li, I., Roberts, L. R. & Chan, C. Elevated free fatty acid uptake via CD36 promotes epithelial-mesenchymal transition in hepatocellular carcinoma. *Sci. Rep.* **5**, 14752 (2015).
101. Rahaman, S. O. *et al.* A CD36-dependent signaling cascade is necessary for macrophage foam cell formation. *Cell Metab.* **4**, 211–221 (2006).
102. Zhao, W. *et al.* Candidate anti-metastasis drugs suppress the metastatic capacity of breast cancer cells by reducing membrane fluidity. *Cancer Res.* **76**, 2037–2049 (2016).
103. Folkman, J. Role of angiogenesis in tumor growth and metastasis. *Semin. Oncol.* **29**, 15–18 (2002).
104. Kazlauskas, A. Lysophosphatidic acid contributes to angiogenic homeostasis. *Exp. Cell Res.* **333**, 166–170 (2015).
105. Mendelson, K., Evans, T. & Hla, T. Sphingosine 1-phosphate signalling. *Development* **141**, 5–9 (2014).
106. Schoors, S. *et al.* Fatty acid carbon is essential for dNTP synthesis in endothelial cells. *Nature* **520**, 192–197 (2015).
107. Fooroot, F. S. *et al.* Fatty acid activated PPAR $\gamma$  promotes tumorigenicity of prostate cancer cells by up regulating VEGF via PPAR responsive elements of the promoter. *Oncotarget* **7**, 9322–9339 (2016).
108. Teng, M. W., Galon, J., Fridman, W. H. & Smyth, M. J. From mice to humans: developments in cancer immunoeediting. *J. Clin. Invest.* **125**, 3338–3346 (2015).
109. Kalinski, P. Regulation of immune responses by prostaglandin E2. *J. Immunol.* **188**, 21–28 (2012).
110. Luan, B. *et al.* CREB pathway links PGE2 signaling with macrophage polarization. *Proc. Natl Acad. Sci. USA* **112**, 15642–15647 (2015).



111. Chang, C. H. *et al.* Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* **162**, 1229–1241 (2015).  
**This study provided evidence of the competition between cancer cells and immune cells for nutrients within the tumour microenvironment.**
112. Wang, R. & Green, D. R. Metabolic checkpoints in activated T cells. *Nat. Immunol.* **13**, 907–915 (2012).
113. Baginska, J. *et al.* The critical role of the tumor microenvironment in shaping natural killer cell-mediated anti-tumor immunity. *Front. Immunol.* **4**, 490 (2013).
114. Kleinfeld, A. M. & Okada, C. Free fatty acid release from human breast cancer tissue inhibits cytotoxic T-lymphocyte-mediated killing. *J. Lipid Res.* **46**, 1983–1990 (2005).
115. Ma, C. *et al.* NAFLD causes selective CD4<sup>+</sup> T lymphocyte loss and promotes hepatocarcinogenesis. *Nature* **531**, 253–257 (2016).
116. Kinlaw, W. B., Baures, P. W., Lupien, L. E., Davis, W. L. & Kuemmerle, N. B. Fatty acids and breast cancer: make them on site or have them delivered. *J. Cell. Physiol.* **231**, 2128–2141 (2016).
117. Flavin, R., Zadra, G. & Loda, M. Metabolic alterations and targeted therapies in prostate cancer. *J. Pathol.* **223**, 283–294 (2011).
118. Pizer, E. S. *et al.* Inhibition of fatty acid synthesis delays disease progression in a xenograft model of ovarian cancer. *Cancer Res.* **56**, 1189–1193 (1996).
119. Pizer, E. S. *et al.* Malonyl-coenzyme-A is a potential mediator of cytotoxicity induced by fatty-acid synthase inhibition in human breast cancer cells and xenografts. *Cancer Res.* **60**, 213–218 (2000).
120. Menendez, J. A. *et al.* Inhibition of fatty acid synthase (FAS) suppresses HER2/neu (erbB-2) oncogene overexpression in cancer cells. *Proc. Natl Acad. Sci. USA* **101**, 10715–10720 (2004).
121. Pizer, E. S., Chrest, F. J., DiGiuseppe, J. A. & Han, W. F. Pharmacological inhibitors of mammalian fatty acid synthase suppress DNA replication and induce apoptosis in tumor cell lines. *Cancer Res.* **58**, 4611–4615 (1998).
122. Li, J. N. *et al.* Pharmacological inhibition of fatty acid synthase activity produces both cytostatic and cytotoxic effects modulated by p53. *Cancer Res.* **61**, 1493–1499 (2001).
123. Zhou, W. *et al.* Fatty acid synthase inhibition triggers apoptosis during S phase in human cancer cells. *Cancer Res.* **63**, 7330–7337 (2003).
124. Menendez, J. A., Vellon, L., Colomer, R. & Lupu, R. Pharmacological and small interference RNA-mediated inhibition of breast cancer-associated fatty acid synthase (oncogenic antigen-519) synergistically enhances Taxol (paclitaxel)-induced cytotoxicity. *Int. J. Cancer* **115**, 19–35 (2005).
125. Gabrielson, E. W., Pinn, M. L., Testa, J. R. & Kuhajda, F. P. Increased fatty acid synthase is a therapeutic target in mesothelioma. *Clin. Cancer Res.* **7**, 153–157 (2001).
126. Horiguchi, A. *et al.* Pharmacological inhibitor of fatty acid synthase suppresses growth and invasiveness of renal cancer cells. *J. Urol.* **180**, 729–736 (2008).
127. Relat, J. *et al.* Different fatty acid metabolism effects of (-)-epigallocatechin-3-gallate and C75 in adenocarcinoma lung cancer. *BMC Cancer* **12**, 280 (2012).
128. Chen, H. W., Chang, Y. F., Chuang, H. Y., Tai, W. T. & Hwang, J. J. Targeted therapy with fatty acid synthase inhibitors in a human prostate carcinoma LNCaP/ tk-luc-bearing animal model. *Prostate Cancer Prostat. Dis.* **15**, 260–264 (2012).
129. Alli, P. M., Pinn, M. L., Jaffee, E. M., McFadden, J. M. & Kuhajda, F. P. Fatty acid synthase inhibitors are chemopreventive for mammary cancer in neu-N transgenic mice. *Oncogene* **24**, 39–46 (2005).
130. Wang, X. & Tian, W. Green tea epigallocatechin gallate: a natural inhibitor of fatty-acid synthase. *Biochem. Biophys. Res. Commun.* **288**, 1200–1206 (2001).
131. Loftus, T. M. *et al.* Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science* **288**, 2379–2381 (2000).
132. Shimokawa, T., Kumar, M. V. & Lane, M. D. Effect of a fatty acid synthase inhibitor on food intake and expression of hypothalamic neuropeptides. *Proc. Natl Acad. Sci. USA* **99**, 66–71 (2002).
133. Cha, S. H., Hu, Z., Chohan, S. & Lane, M. D. Inhibition of hypothalamic fatty acid synthase triggers rapid activation of fatty acid oxidation in skeletal muscle. *Proc. Natl Acad. Sci. USA* **102**, 14557–14562 (2005).
134. Li, L. *et al.* Inactivation of fatty acid synthase impairs hepatocarcinogenesis driven by AKT in mice and humans. *J. Hepatol.* **64**, 333–341 (2016).
135. Knobloch, M. *et al.* Metabolic control of adult neural stem cell activity by Fasn-dependent lipogenesis. *Nature* **493**, 226–230 (2013).  
**This study demonstrated that FASN is highly active in proliferating adult neural stem cell progenitors.**
136. Bauer, D. E., Hatzivassiliou, G., Zhao, F., Andreadis, C. & Thompson, C. B. ATP citrate lyase is an important component of cell growth and transformation. *Oncogene* **24**, 6314–6322 (2005).
137. Zaidi, N., Royaux, I., Swinnen, J. V. & Smans, K. ATP citrate lyase knockdown induces growth arrest and apoptosis through different cell- and environment-dependent mechanisms. *Mol. Cancer Ther.* **11**, 1925–1935 (2012).
138. Wellen, K. E. *et al.* ATP-citrate lyase links cellular metabolism to histone acetylation. *Science* **324**, 1076–1080 (2009).
139. Schug, Z. T. *et al.* Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress. *Cancer Cell* **27**, 57–71 (2015).
140. Comerford, S. A. *et al.* Acetate dependence of tumors. *Cell* **159**, 1591–1602 (2014).
141. Yoshii, Y. *et al.* Cytosolic acetyl-CoA synthetase affected tumor cell survival under hypoxia: the possible function in tumor acetyl-CoA/acetate metabolism. *Cancer Sci.* **100**, 821–827 (2009).
142. Mashimo, T. *et al.* Acetate is a bioenergetic substrate for human glioblastoma and brain metastases. *Cell* **159**, 1603–1614 (2014).
143. Schug, Z. T., Vande Voorde, J. & Gottlieb, E. Metabolic fate of acetate in cancer. *Nat. Rev. Cancer* <https://doi.org/10.1038/nrc.2016.87> (2016).
144. Wang, C. *et al.* Acetyl-CoA carboxylase- $\alpha$  inhibitor TOFA induces human cancer cell apoptosis. *Biochem. Biophys. Res. Commun.* **385**, 302–306 (2009).
145. Brusselmanns, K., De Schrijver, E., Verhoeven, G. & Swinnen, J. V. RNA interference-mediated silencing of the acetyl-CoA-carboxylase- $\alpha$  gene induces growth inhibition and apoptosis of prostate cancer cells. *Cancer Res.* **65**, 6719–6725 (2005).
146. Chajes, V., Cambot, M., Moreau, K., Lenoir, G. M. & Joulin, V. Acetyl-CoA carboxylase  $\alpha$  is essential to breast cancer cell survival. *Cancer Res.* **66**, 5287–5294 (2006).
147. Jeon, S. M., Chandel, N. S. & Hay, N. AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress. *Nature* **485**, 661–665 (2012).
148. Griffiths, B. *et al.* Sterol regulatory element binding protein-dependent regulation of lipid synthesis supports cell survival and tumor growth. *Cancer Metab.* **1**, 3 (2013).
149. Williams, K. J. *et al.* An essential requirement for the SCAP/SREBP signaling axis to protect cancer cells from lipotoxicity. *Cancer Res.* **73**, 2850–2862 (2013).
150. Young, R. M. *et al.* Dysregulated mTORC1 renders cells critically dependent on desaturated lipids for survival under tumor-like stress. *Genes Dev.* **27**, 1115–1131 (2013).  
**References 148–150 demonstrated that inhibition of FA desaturation leads to the induction of ER stress.**
151. Sanchez-Alvarez, M. *et al.* Signaling networks converge on TORC1-SREBP activity to promote endoplasmic reticulum homeostasis. *PLoS ONE* **9**, e101164 (2014).
152. Guo, D. *et al.* EGFR signaling through an Akt-SREBP-1-dependent, rapamycin-resistant pathway sensitizes glioblastomas to antilipogenic therapy. *Sci. Signal.* **2**, ra82 (2009).
153. Cheng, C. *et al.* Glucose-mediated N-glycosylation of SCAP is essential for SREBP-1 activation and tumor growth. *Cancer Cell* **28**, 569–581 (2015).  
**This study provided mechanistic evidence for SREBP activation in glycolytic cancer cells through enhanced glycosylation of SCAP. It also demonstrated that SCAP depletion reduces orthotopic glioblastoma growth.**
154. Zelcer, N., Hong, C., Boyadjian, R. & Tontonoz, P. LXR regulates cholesterol uptake through Idol-dependent ubiquitination of the LDL receptor. *Science* **325**, 100–104 (2009).
155. Bovenga, F., Sabba, C. & Moschetta, A. Uncoupling nuclear receptor LXR and cholesterol metabolism in cancer. *Cell Metab.* **21**, 517–526 (2015).
156. Guo, D. *et al.* An LXR agonist promotes GBM cell death through inhibition of an EGFR/AKT/SREBP-1/LDLR-dependent pathway. *Cancer Discov.* **1**, 442–456 (2011).
157. Flaveny, C. A. *et al.* Broad anti-tumor activity of a small molecule that selectively targets the warburg effect and lipogenesis. *Cancer Cell* **28**, 42–56 (2015).  
**This study showed that inhibition of SREBP by an LXR antagonist blocks glycolysis and lipogenesis in cancer cells and inhibits tumour cell growth.**
158. Kamisuki, S. *et al.* A small molecule that blocks fat synthesis by inhibiting the activation of SREBP. *Chem. Biol.* **16**, 882–892 (2009).
159. Li, X., Chen, Y. T., Hu, P. & Huang, W. C. Fatostatin displays high antitumor activity in prostate cancer by blocking SREBP-regulated metabolic pathways and androgen receptor signaling. *Mol. Cancer Ther.* **13**, 855–866 (2014).
160. Li, X., Wu, J. B., Chung, L. W. & Huang, W. C. Anti-cancer efficacy of SREBP inhibitor, alone or in combination with docetaxel, in prostate cancer harboring p53 mutations. *Oncotarget* **6**, 41018–41032 (2015).
161. Tang, J. J. *et al.* Inhibition of SREBP by a small molecule, betulin, improves hyperlipidemia and insulin resistance and reduces atherosclerotic plaques. *Cell Metab.* **13**, 44–56 (2011).
162. Krol, S. K., Kielbus, M., Rivero-Muller, A. & Stepulak, A. Comprehensive review on betulin as a potent anticancer agent. *Biomed. Res. Int.* **2015**, 584189 (2015).
163. Matsuda, M. *et al.* SREBP cleavage-activating protein (SCAP) is required for increased lipid synthesis in liver induced by cholesterol deprivation and insulin elevation. *Genes Dev.* **15**, 1206–1216 (2001).
164. Winter, G. E. *et al.* DRUG DEVELOPMENT. Phthalimide conjugation as a strategy for *in vivo* target protein degradation. *Science* **348**, 1376–1381 (2015).
165. Marien, E. *et al.* Phospholipid profiling identifies acyl chain elongation as a ubiquitous trait and potential target for the treatment of lung squamous cell carcinoma. *Oncotarget* **7**, 12582–12597 (2016).
166. Mason, P. *et al.* SCD1 inhibition causes cancer cell death by depleting mono-unsaturated fatty acids. *PLoS ONE* **7**, e33823 (2012).
167. Hess, D., Chisholm, J. W. & Igal, R. A. Inhibition of stearyl-CoA desaturase activity blocks cell cycle progression and induces programmed cell death in lung cancer cells. *PLoS ONE* **5**, e11394 (2010).
168. Scaglia, N., Chisholm, J. W. & Igal, R. A. Inhibition of stearyl-CoA desaturase-1 inactivates acetyl-CoA carboxylase and impairs proliferation in cancer cells: role of AMPK. *PLoS ONE* **4**, e6812 (2009).
169. Roongta, U. V. *et al.* Cancer cell dependence on unsaturated fatty acids implicates stearyl-CoA desaturase as a target for cancer therapy. *Mol. Cancer Res.* **9**, 1551–1561 (2011).
170. Fritz, V. *et al.* Abrogation of *de novo* lipogenesis by stearyl-CoA desaturase 1 inhibition interferes with oncogenic signaling and blocks prostate cancer progression in mice. *Mol. Cancer Ther.* **9**, 1740–1754 (2010).
171. Scaglia, N. & Igal, R. A. Inhibition of Stearyl-CoA Desaturase 1 expression in human lung adenocarcinoma cells impairs tumorigenesis. *Int. J. Oncol.* **33**, 839–850 (2008).
172. Budhu, A. *et al.* Integrated metabolite and gene expression profiles identify lipid biomarkers associated with progression of hepatocellular carcinoma and patient outcomes. *Gastroenterology* **144**, 1066–1075 (2013).
173. Singh, A. & Settleman, J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. *Oncogene* **29**, 4741–4751 (2010).
174. Menendez, J. A., Lupu, R. & Colomer, R. Inhibition of tumor-associated fatty acid synthase hyperactivity induces synergistic chemosensitization of HER-2/neu-overexpressing human breast cancer cells to docetaxel (taxotere). *Breast Cancer Res. Treat.* **84**, 183–195 (2004).
175. Vazquez-Martin, A., Ropero, S., Brunet, J., Colomer, R. & Menendez, J. A. Inhibition of Fatty Acid Synthase (FASN) synergistically enhances the efficacy of 5-fluorouracil in breast carcinoma cells. *Oncol. Rep.* **18**, 973–980 (2007).
176. Liu, H., Liu, Y. & Zhang, J. T. A new mechanism of drug resistance in breast cancer cells: fatty acid synthase overexpression-mediated palmitate overproduction. *Mol. Cancer Ther.* **7**, 263–270 (2008).

177. Ebos, J. M. & Kerbel, R. S. Antiangiogenic therapy: impact on invasion, disease progression, and metastasis. *Nat. Rev. Clin. Oncol.* **8**, 210–221 (2011).
178. Sounni, 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.**
179. Golay, A., Swislocki, A. L., Chen, Y. D., Jaspán, J. B. & Reaven, G. M. Effect of obesity on ambient plasma glucose, free fatty acid, insulin, growth hormone, and glucagon concentrations. *J. Clin. Endocrinol. Metab.* **63**, 481–484 (1986).
180. Lewis, D. Y. *et al.* Late imaging with [<sup>11</sup>C]acetate improves detection of tumor fatty acid synthesis with PET. *J. Nucl. Med.* **55**, 1144–1149 (2014).
181. DeGrado, T. R., Kitapci, M. T., Wang, S., Ying, J. & Lopaschuk, G. D. Validation of 18F-fluoro-4-thia-palmitate as a PET probe for myocardial fatty acid oxidation: effects of hypoxia and composition of exogenous fatty acids. *J. Nucl. Med.* **47**, 173–181 (2006).
182. Krahmer, N., Guo, Y., Farese, R. V. Jr & Walther, T. C. SnapShot: lipid droplets. *Cell* **139**, 1024–1024.e1 (2009).
183. Zechner, R. FAT FLUX: enzymes, regulators, and pathophysiology of intracellular lipolysis. *EMBO Mol. Med.* **7**, 359–362 (2015).
184. Vamecq, J., Cherkaoui-Malki, M., Andreoletti, P. & Latruffe, N. The human peroxisome in health and disease: the story of an oddity becoming a vital organelle. *Biochimie* **98**, 4–15 (2014).
185. Carling, D., Clarke, P. R., Zammit, V. A. & Hardie, D. G. Purification and characterization of the AMP-activated protein kinase. Copurification of acetyl-CoA carboxylase kinase and 3-hydroxy-3-methylglutaryl-CoA reductase kinase activities. *Eur. J. Biochem.* **186**, 129–136 (1989).
186. Carracedo, A., Cantley, L. C. & Pandolfi, P. P. Cancer metabolism: fatty acid oxidation in the limelight. *Nat. Rev. Cancer* **13**, 227–232 (2013).
187. Zaugg, K. *et al.* Carnitine palmitoyltransferase 1C promotes cell survival and tumor growth under conditions of metabolic stress. *Genes Dev.* **25**, 1041–1051 (2011).
188. Park, J. H. *et al.* Fatty acid oxidation-driven src links mitochondrial energy reprogramming and oncogenic properties in triple-negative breast cancer. *Cell Rep.* **14**, 2154–2165 (2016).
189. Szutowicz, A., Kwiatkowski, J. & Angielski, S. Lipogenetic and glycolytic enzyme activities in carcinoma and nonmalignant diseases of the human breast. *Br. J. Cancer* **39**, 681–687 (1979).
190. Hietanen, E., Punnonen, K., Punnonen, R. & Auvinen, O. Fatty acid composition of phospholipids and neutral lipids and lipid peroxidation in human breast cancer and lipoma tissue. *Carcinogenesis* **7**, 1965–1969 (1986).
191. Yokoyama, C. *et al.* SREBP-1, a basic-helix-loop-helix-leucine zipper protein that controls transcription of the low density lipoprotein receptor gene. *Cell* **75**, 187–197 (1993).
192. Hua, X. *et al.* SREBP-2, a second basic-helix-loop-helix-leucine zipper protein that stimulates transcription by binding to a sterol regulatory element. *Proc. Natl Acad. Sci. USA* **90**, 11603–11607 (1993).
193. Tontonoz, P., Kim, J. B., Graves, R. A. & Spiegelman, B. M. ADD1: a novel helix-loop-helix transcription factor associated with adipocyte determination and differentiation. *Mol. Cell. Biol.* **13**, 4753–4759 (1993).
194. Bennett, M. K., Lopez, J. M., Sanchez, H. B. & Osborne, T. F. Sterol regulation of fatty acid synthase promoter. Coordinate feedback regulation of two major lipid pathways. *J. Biol. Chem.* **270**, 25578–25583 (1995).
195. Swinnen, J. V., Esquenet, M., Goossens, K., Heyns, W. & Verhoeven, G. Androgens stimulate fatty acid synthase in the human prostate cancer cell line LNCaP. *Cancer Res.* **57**, 1086–1090 (1997).
196. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646–674 (2011).
197. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT02223247> (2014).
198. Buckley, D., Heuer, T., O'Farrell, M., McCulloch, B. & Kemble, G. Translational studies of a first-in-class FASN inhibitor, TVB-2640, linking preclinical studies to clinical laboratory observations in solid tumor patients. *Mol. Cell. Res.* **14** (Suppl. 1), Abstr. A75 (2016).
199. Shaw, G. *et al.* Therapeutic fatty acid synthase inhibition in prostate cancer and the use of 11c-acetate to monitor therapeutic effects. *J. Urol.* **189**, E208–E209 (2013).
200. Zhou, W. *et al.* Fatty acid synthase inhibition activates AMP-activated protein kinase in SKOV3 human ovarian cancer cells. *Cancer Res.* **67**, 2964–2971 (2007).
201. Orita, H. *et al.* Selective inhibition of fatty acid synthase for lung cancer treatment. *Clin. Cancer Res.* **13**, 7139–7145 (2007).
202. El Meskini, R. *et al.* Fatty acid synthase inhibition for ovarian cancer. *Cancer Res.* **68**, Supplement 5667 [http://cancerres.aacrjournals.org/content/68/9\\_Supplement/5667](http://cancerres.aacrjournals.org/content/68/9_Supplement/5667) (2008).
203. Orita, H. *et al.* Inhibition of fatty acid synthase by C247 for lung cancer treatment. *Cancer Res.* **65**, Supplement 2380 [http://cancerres.aacrjournals.org/content/65/9\\_Supplement/558.2](http://cancerres.aacrjournals.org/content/65/9_Supplement/558.2) (2005).
204. Pizer, E. S. *et al.* Inhibition of fatty acid synthesis induces programmed cell death in human breast cancer cells. *Cancer Res.* **56**, 2745–2747 (1996).
205. Kridel, S. J., Axelrod, F., Rozenkrantz, N. & Smith, J. W. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. *Cancer Res.* **64**, 2070–2075 (2004).
206. Carvalho, M. A. *et al.* Fatty acid synthase inhibition with Orlistat promotes apoptosis and reduces cell growth and lymph node metastasis in a mouse melanoma model. *Int. J. Cancer* **123**, 2557–2565 (2008).
207. Sadowski, M. C. *et al.* The fatty acid synthase inhibitor triclosan: repurposing an anti-microbial agent for targeting prostate cancer. *Oncotarget* **5**, 9362–9381 (2014).
208. Lee, H. R., Hwang, K. A., Nam, K. H., Kim, H. C. & Choi, K. C. Progression of breast cancer cells was enhanced by endocrine-disrupting chemicals, triclosan and octylphenol, via an estrogen receptor-dependent signaling pathway in cellular and mouse xenograft models. *Chem. Res. Toxicol.* **27**, 834–842 (2014).
209. Beckers, A. *et al.* Chemical inhibition of acetyl-CoA carboxylase induces growth arrest and cytotoxicity selectively in cancer cells. *Cancer Res.* **67**, 8180–8187 (2007).
210. Samudio, I. *et al.* Pharmacologic inhibition of fatty acid oxidation sensitizes human leukemia cells to apoptosis induction. *J. Clin. Invest.* **120**, 142–156 (2010).
211. Tirado-Velez, J. M., Joumady, I., Saez-Benito, A., Cozar-Castellano, I. & Perdomo, G. Inhibition of fatty acid metabolism reduces human myeloma cells proliferation. *PLoS ONE* **7**, e46484 (2012).
212. Liu, P. P. *et al.* Elimination of chronic lymphocytic leukemia cells in stromal microenvironment by targeting CPT with an antiangiogenic drug perhexiline. *Oncogene* <https://dx.doi.org/10.1038/onc.2016.103> (2016).
213. Von Roemeling, C. A. *et al.* Stearoyl-CoA desaturase 1 is a novel molecular therapeutic target for clear cell renal cell carcinoma. *Clin. Cancer Res.* **19**, 2368–2380 (2013).

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**Competing interests statement**

The authors declare no competing interests.

**DATABASES**

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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.