Chapter

Roles of Lipids in Cancer

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Abstract

The term 'lipids' refers to a class of biological molecules primarily composed of hydrocarbons such as fatty acids, glycerolipids, sphingolipids and sterol lipids. Lipids take part in a variety of physiological functions and have specific roles depending on their chemical structure and localisation within or outside cells. For example, glycerolipids (e.g. triglycerides) are often used as energy stores, sterol lipids (e.g. cholesterol) and glycerophospholipids as structural components of cell membranes (e.g. the lipid bilayer), and sphingolipids as part of a signalling cascade. Since lipids are a source of energy and basic building block of all living cells, it is not surprising that development of cancer (i.e. uncontrolled proliferation of cells) is closely tied to the metabolism of lipids. This notion is supported by studies into the reprogrammed metabolic machinery in cancer cells, and also cell and animal model experiments showing that cancer growth and metastasis can be induced or inhibited by the exogenous addition of lipids. Here, we review how cancer cells can alter their lipid metabolism to meet their metabolic requirements, and the potential tumorigenic and tumour-suppressive mechanisms in which lipids are involved.

Keywords: lipids, cancer, metabolic reprogramming, signalling, autophagy, tumour development, cancer progression

1. Lipids in cancer

1.1 Lipid metabolism in tumours

Tumours can be simplistically described as masses of uncontrolled abnormal cellular growth. As they rapidly divide and proliferate, tumours require a steady source of energy and nutrients to accumulate biomass, and compete with healthy cells over a limited supply of essential cellular building blocks. Many cancers have adapted to their harsh environments by changing their metabolic profiles (the term 'reprogramming' is commonly used to describe this) to support growth and improve their chances of survival [1], among which the most well described is arguably their preference to perform glycolysis under aerobic conditions, an observation known as the Warburg effect [2]. In normal cells, glucose is hydrolysed via glycolysis, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation to extract the maximum amount of energy in the form of adenosine triphosphate (ATP). This process utilises oxygen as the terminal electron acceptor during oxidative phosphorylation. In the absence of oxygen, glucose is still broken down to pyruvate via glycolysis, but is subsequently converted to lactate instead of being passed through the TCA cycle and oxidative phosphorylation. Metabolising glucose through glycolysis and fermentation into lactate results in smaller amounts of ATP compared to oxidative phosphorylation, however, tumour cells tend to prefer

this path even in the presence of oxygen (i.e. the Warburg effect). A hypothesis to explain this preference suggests that instead of completely exhausting the carbon molecules in glucose through aerobic respiration (oxidative phosphorylation), highly proliferating cells need to conserve their carbon sources for the purpose of accumulating biomass [2, 3]. Vander Heiden and colleagues calculated the number of ATP and reduced nicotinamide adenine dinucleotide (NADH) molecules produced by glucose and compared these to the amount required for synthesis of macromolecules such as fatty acids, and concluded that proliferating tumours cannot utilise all their glucose stores for ATP production alone. The preference for glycolysis therefore could serve to increase availability of carbon-based precursors of biomolecules such as lipids, amino acids and nucleic acids that would otherwise be converted to carbon dioxide (CO_2) through respiration via the TCA cycle and oxidative phosphorylation.

By reducing the loss of carbon through respiration, tumour cells can utilise this saved pool for synthesising basic cellular building blocks necessary for sustaining their proliferation. One such example is the synthesis of fatty acids and other lipid molecules derived from the modification of fatty acids. Fatty acids and their derivatives have indispensable roles in cell biology; a few key functions include formation of the basic structure of the cell membrane, as an energy storage pool and as mediators in cellular signalling cascades. Lipids are typically obtained from dietary sources or synthesised in living cells beginning from the precursor molecule acetyl-coA. In most eukaryotic cells, pyruvate is produced from the breakdown of glucose via glycolysis. It is then funnelled into the mitochondria in which the enzyme pyruvate dehydrogenase converts pyruvate to acetyl-coA. Acetyl-coA is subsequently converted into citrate by citrate synthase (first step in the TCA cycle), a step necessary to transport acetyl-coA in the form of citrate from the mitochondria into the cytosol which is the site of fatty acid synthesis. Citrate is transported out of the mitochondria and converted back into acetyl-coA by ATP citrate lyase (ACLY) in the cytosol. Next, acetyl-coA is carboxylated by acetyl-coA carboxylase (ACC) to form malonyl-coA, and both precursors are then attached to an acyl carrier protein and repeatedly elongated with units of carbons from additional malonyl-coA molecules. This elongation is performed by fatty acid synthase (FASN) to produce a 16-carbon molecule termed palmitic acid. Palmitic acid can be further desaturated and/or elongated to produce unsaturated fatty acid derivatives which serve as building blocks for the synthesis of other lipids such as phosphoglycerides, phosphoinositides, eicosanoids and sphingolipids (summarised in **Figure 1**, reviewed in [4]. Separately, acetyl-coA is also used for the synthesis of cholesterol through the mevalonate pathway. This process involves first converting acetyl-coA into lanosterol (via intermediates including 3-hydroxy-3-methylglutaryl coA, mevalonate, isopentenyl pyrophosphate, farnesyl pyrophosphate and squalene), which is then transformed into cholesterol through a multi-step enzymatic process.

Studies have indicated that the biosynthesis of basic cellular building blocks including proteins, fatty acids and nucleic acids is modified and/or upregulated in [5, 6], indicating that the metabolism in highly proliferating cancer cells is likely altered to support their abnormal growth. Lipids and fatty acids in particular are required for the biosynthesis and modification of the lipid bilayer membrane in newly formed cells [7], and also for other roles related to cell signalling and tumour survival. Consistent with the fatty acid biosynthesis pathway, tumours primarily obtain carbon acyl fatty acid precursors from glucose [8, 9]. To increase the production of fatty acids and other lipids, tumour cells hijack the fatty acid biosynthesis pathway to their advantage. Component enzymes in the pathway (ACLY, ACC and FASN) are commonly upregulated in tumours [10–13], and inhibition or silencing

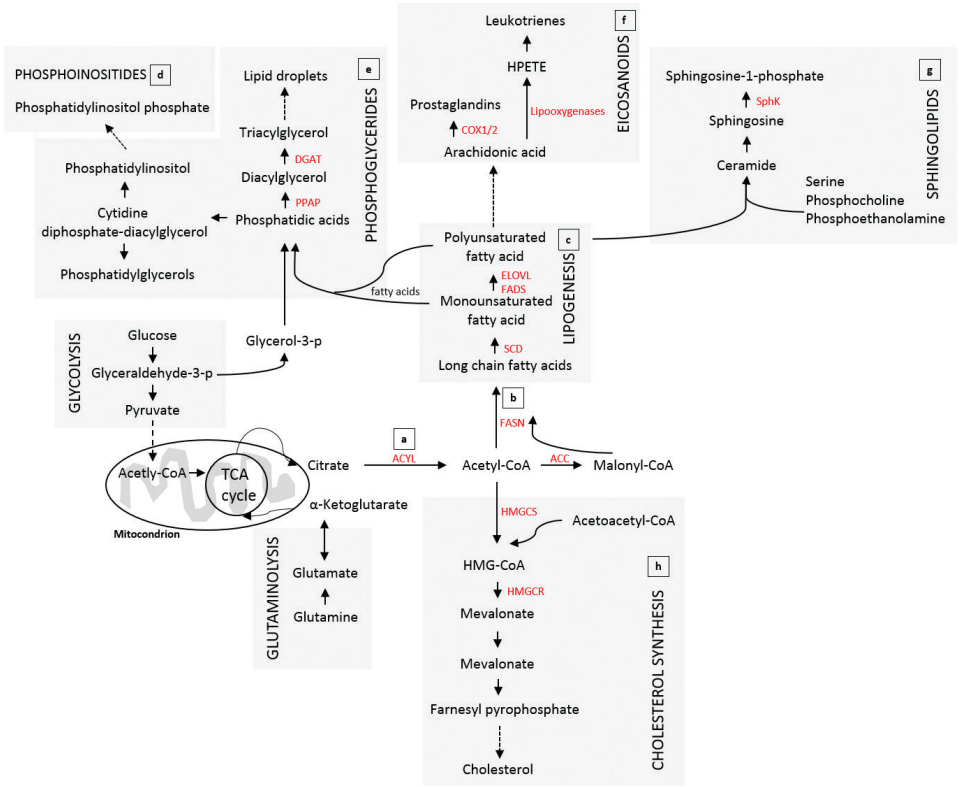

Figure 1.
Lipid biosynthesis. Schematic representation of the pathways involved in the synthesis of fatty acids, cholesterols, phosphoglycerides, eicosanoids, and sphingolipids. Enzymes involved in catalysing the process are labelled in red. (a) Citrate derived from the tricarboxylic acid (TCA) cycle is first converted to acetyl-CoA by ATP citrate lyase (ACYL). (b) For fatty acid synthesis, acetyl-CoA carboxylase (ACC) adds a carboxyl group to convert acetyl-CoA to malonyl-CoA. Repeated condensation of acetyl-CoA and malonyl-CoA catalysed by fatty acid synthase (FASN) results in a 16-carbon fatty acid chain. After which, the 16-carbon fatty acid chain is cleaved by thioesterase to generate long chain fatty acids such as palmitic acid, stearic acid, and oleic acid. The addition of a double bond by stearoyl-CoA desaturase (SCD) yields monounsaturated fatty acids. (c) Subsequent elongation and desaturation, catalysed by enzymes fatty acid elongase (ELOVL) and fatty acid desaturase (FADS) produces a pool of fatty acids with different saturation levels. Essential fatty acids can also be obtained from dietary intake. (d–g) Subsequent modification generates different types of lipids. (d and e) In glycerolipid biosynthesis, saturated and unsaturated fatty acids combine with glycerol-3-phosphate, a reaction highly dependent on glycerol-3-phosphate acyltransferase (GPAT) to generate (d) phosphoinositides and (e) phosphoglycerides. (f) Eicosanoids are signalling molecules made by oxidation of polyunsaturated fatty acids such as arachidonic acid. Downstream, multiple families of eicosanoids such as prostaglandins and leukotrienes can be generated. (g) Sphingolipids contains acyl chains and polar head groups derived from serine, phosphocholine, and phosphoethanolamine. Ceramide, sphingomyelin, and sphingosine are common intermediates of the sphingolipid metabolic pathway (h) cholesterol synthesis is regulated by a series of conversion and addition of acyl groups by enzymes 3-hydroxy-3-methylglutarate-CoA synthase (HMGCS) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). Subsequent modifications yield farnesyl-pyrophosphate, an important intermediate for protein prenylation. Cholesterol also forms the structural backbone of hormone synthesis in the cell. Abbreviations used in the figure: coenzyme A (-CoA), prostaglandin-endoperoxide synthase (COX1/2), diacylglycerol O-acyltransferase (DGAT), 3-hydroxyl-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA), arachidonic acid 5-hydroperoxide (HPETE), and phosphatidic acid phosphatase (PPAP).

of these enzymes has been demonstrated to restrict growth of cancerous cells [14–16]. The upregulation of these fatty acid synthesis-related enzymes is achieved through signalling by the mammalian target of rapamycin (mTOR) complex 1 and transcription factors called sterol regulatory element-binding proteins (SREBPs). SREBPs exert transcriptional control over various fatty acid, cholesterol, triglycerides and phospholipid synthesis and uptake genes [17] and are regulated by mTOR complex 1, a nutrient and growth factor responsive kinase [18]. Previous studies

conducted in various cancers have implicated deregulation of mTOR signalling in mediating proliferation of cancer cells (reviewed in [19, 20]). More specifically, mTOR and SREBPs have been shown to increase lipid biosynthesis through Akt signalling thereby promoting proliferation in cancer cells [21]. The signalling by mTOR complex 1 also leads to upregulated fatty acid biosynthesis in cancer cells either by activating SREBPs via S6 kinase [22] or phosphorylating (downregulating) the SREBP inhibitor Lipin 1 [18]. In addition to lipids, mTOR complex 1 signalling is also implicated in promoting biosynthesis of proteins and nucleotides [23–25]. Taken together, these findings indicate that the deregulation of mTOR complex 1 plays a central metabolic role in promoting growth and proliferation of cancer cells by allowing them to 'reprogram' their metabolism. Indeed, there are studies into the potential use of mTOR inhibitors as cancer therapy drugs given its importance in the development of cancer.

1.2 Lipids as promoters of cancer

Early experiments have established that the lipid composition of tumour tissues is distinct from normal healthy cells [26–29]. Their lipid composition differs depending on the type of tumour tissue and possibly also correlates with tumour stage and malignancy characteristics, as recently demonstrated in a comparison of membrane lipid composition between six human breast cancer cell lines and healthy mammary epithelia [30]. These and other similar studies led to the notion that lipids could play an active role in cancers in addition to their basic function of maintaining structural integrity of the lipid bilayer membrane. One such example is a class of lipids termed sphingolipids. Sphingolipids are lipid molecules that contain an amino alcohol group in their backbones, and depending on additional substitutions with fatty acid residues or phosphocholine, form sphingolipid derivatives such as ceramides and sphingomyelins. The basic role of sphingolipids is to augment fluidity and barrier function of the lipid bilayer cell membrane in which they normally reside in the outer leaflet. Sphingolipids, in particular sphingosine-1-phosphate (S1P), have been demonstrated to promote cell survival during tumorigenesis as inhibition of either upstream fatty acid or specifically sphingolipid synthesis restricts tumour growth [31]. Sphingosine can be synthesised from condensation of palmitic acid with the amino acid serine, or from the cleaving of fatty acid residues from ceramides by ceramidase. The resulting sphingosine is phosphorylation by sphingosine kinase, producing S1P. S1P signalling interacts with histone deacetylase 1, 2 (HDAC1 and HDAC2) and telomerase to control many key cellular process involving cellular growth, proliferation, migration and invasion (reviewed by [32, 33]; see section below on lipids as signalling mediators in cancer), thus its metabolism and related enzymes are an area of considerable research interest.

A second aspect to the role of lipids in promoting cancer is the influence of exogenous sources of lipids in facilitating tumorigenesis and metastasis. Numerous studies have experimented with high lipid content diets using mouse models and reported increases in tumour growth and/or metastasis, implicating high fat ketogenic diets [34–36] or specific lipids such as cholesterol [37] or palmitic acid [38] in promoting cancer. There is a variety of mechanisms by which high concentrations of dietary lipids can exert a tumorigenic effect. According to Liśkiewicz and colleagues, their high fat ketogenic diet administered *ad libitum* to mice led to activation of ERK1/2 which controls cell proliferation, differentiation and survival [39], as well as elevated mTOR signalling in renal tumours [34]. In a different study, high fat diets caused acetoacetate levels in the serum of recipient mice to increase, subsequently leading to enhanced tumour growth of xenograft human melanoma

cells with a V600E mutation in the BRAF gene [35]. Another mechanism by which high fat diets could enhance tumour metastasis is through the Ras-Raf-MEK-ERK mitogen-activated protein kinase (MAPK) pathway which was recently shown to activate SREBPs and therefore lipogenesis in metastatic human prostate cancer [36]. More examples of specific lipid groups linked to cancer include cholesterol and palmitic acid as mentioned above. The introduction of excess cholesterol either through dietary sources or by genetically increasing cellular cholesterol biosynthesis stimulated growth of intestinal crypt cells, leading to a more than 100-fold increase in the rate of tumour formation in the gastrointestinal tracts of live mice [37]. Similarly, exogenous addition of palmitic acid was shown to increase the invasiveness of human pancreatic cancer cells via a toll-like receptor 4 (TLR4)-mediated pathway [40], promote growth of melanoma cells through Akt signalling [41], and also increase the metastatic potential of human oral carcinoma through membrane-bound fatty acid receptors termed CD36 [38]. These studies collectively suggest that excess dietary lipids are detrimental to health and could exacerbate cancers in addition to obesity; however, whether these findings translate into appreciable risks of cancers in humans remains an open question.

1.3 Lipids as suppressor of cancer

On the other hand, not all classes of lipids appear to stimulate cancer growth and metastasis. There is evidence supporting an inhibitory role of polyunsaturated fatty acids (PUFAs) in cancer development [42–44]; reviewed in [45], although conflicting experimental results do exist [46]; reviewed in [47]. Dietary PUFAs commonly consumed by humans encompass two major groups—the n-3 and n-6 families of PUFAs. These PUFAs are categorised by the position of their first double bond from the methyl end of the fatty acid molecule (n-3 signifying double bond between third and fourth carbon atom, n-6 between sixth and seventh carbon atom). Some common n-3 PUFAs include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and common n-6 ones include linoleic acid (LA) and arachidonic acid (AA). The cancer promoting or inhibitory effects of PUFAs is hypothesised to depend on the relative amounts of n-6 and n-3 administered [48]. Current trends suggest that n-3 PUFAs are beneficial towards reducing cancer, whereas n-6 PUFAs tend to increase risks. An epidemiological survey tracking more than 72,000 female participants and their diets over an average duration of 8 years indicated that individuals consuming higher amounts of n-6 PUFAs relative to n-3 faced increased risks of developing breast cancer [49]. These trends in a large cohort were consistent with previous assessments of the beneficial properties of the n-3 PUFAs EPA [50–52] and DHA [53, 54] in fighting various cancers. The beneficial properties of ALA (also n-3), however, is less established compared to EPA and DHA. Consumption of ALA in mouse models of prostate cancer were shown to reduce cancer growth [46], although another study conducted on human prostate tissue presented evidence that ALA in the prostate was associated with aggressive prostate cancer [47]. The n-6 PUFA LA is commonly studied in the context of breast cancers, although its role is still currently unclear as studies of LA and risk of breast cancer have returned inconsistent results [55, 56]. The other n-6 PUFA, AA, is often studied in the context of prostate cancers and have been shown to increase prostate cancer growth [57, 58], although a meta-analysis of AA and the risk of various cancers including prostate only show weak associations [59]. The exact role of PUFAs in cancers most likely depends on many other factors including cancer cell type, stage and host metabolism of these PUFAs, all of which should be explored in more detail to exploit PUFAs in anticancer therapy.

2. Lipids as signalling mediators in cancer

Many cellular signalling hormones and growth factors have structural components comprising of lipids. Examples of such hormones and factors include prostaglandins, lysophosphatidic acid, and steroid hormones to name a few. Lysophosphatidic acid is a phospholipid derivative that binds G protein coupled receptors (GPCRs) to activate cell proliferation, survival, and migration. As such, tumorigenesis and cancer expansion is commonly attributed to dysregulated lysophosphatidic acid expression and signalling [60]. In addition, autotaxin, a secreted enzyme involved in production of lysophosphatidic acid is associated with hyper proliferation [61] and tumour invasiveness [62]. Overexpression of autotaxin and lysophosphatidic acid receptors was reported in several cancers including glioblastoma [63], prostate [64], and breast cancer [65], all of which overexpression contributed to increased cell motility and invasive potential. Notably, production of either autotaxin or lysophosphatidic acid receptors was sufficient to induce development of high frequency invasive breast tumours [60]. In human liver cancer cells, lysophosphatidic acid has also been shown to bind lysophosphatidic receptor 1 to activate MMP-9 signalling and promote cancer cell invasion [66].

Bioactive sphingolipids form an important class of lipids consisting of sphingosines, ceramides, and other complex sphingolipids such as sphingomyelins and glycosphingolipids. They bind specific protein targets to elicit signalling responses in important cellular events such as growth regulation, cell adhesion, migration, apoptosis, and inflammation [67]. Sphingolipids and its derivatives have been implicated in the regulation of signalling cascades in multiple aspects of cancer pathogenesis and therapy, in either tumour suppression or survival of various cancers [33, 67]. For instance, ceramides are commonly known to suppress tumour growth by mediating cancer cell death via apoptosis, necroptosis or mitophagy [68]. They are synthesised in response to cellular stresses that produce apoptotic signals such as chemotherapy or ultraviolet (UV) radiation [69]. Various modes by which ceramide regulates apoptosis have been proposed. One such example is in radiation-induced apoptosis, during which ceramide channels activate mitochondrial apoptosis through mitochondrial outer membrane permeabilization [70]. On the other hand, S1P is considered to be a pro-survival lipid as it is able to initiate cancer cell proliferation, malignant transformation, prevent apoptosis, and promote resistance to anti-cancer therapies [68, 71, 72]. SIP mediates host-cancer cell communication by engaging G protein-coupled S1P receptor-dependent or -independent signalling to promote tumour migration, survival, and evasion of host immune responses [73].

Prostaglandins are a subclass of eicosanoids. They are synthesised by the oxidation of 20-carbon essential fatty acids catalysed by phospholipases and cyclooxygenase (COX) enzymes. Prostaglandin E2 (PGE(2)) is the most widely studied and has been proposed to directly modulate tumorigenesis in several cancers (reviewed in [74]). For instance, administration of exogenous PGE(2) to F344 rat models resulted in higher incidences and multiplicity of intestinal adenomas [75]. Enhanced colon carcinogenesis was proposed to occur through the activation of PGE(2) signalling, by binding of E-prostanoid (EP) membrane receptors 1–4 [75]. A separate *in vitro* study showed that PGE(2) treatment upregulated epithelial cell proliferation and COX-2 expression in intestinal adenomas, proposed to act via the Ras-mitogen-activated protein kinase signalling pathway [76]. Other than PGE(2), uncontrolled expression of EP has also been reported and as a result affects the outcome of various cancers [77, 78]. For example, Jin and colleagues [79] demonstrated that activation of PGE(2) with EP1 receptor agonist ONO-DI-004, but not antagonist ONO-8711, improved cell viability and migration of liver cancer cells. In Lewis lung carcinoma cells, EP3 was shown to trigger production of MMP-9 and

VEGF, both of which are central regulators of angiogenesis and subsequent metastasis [80], further indicating the role of prostaglandin signalling in cancer progression. Taken together, the modification of signalling pathways by cancer cells affects abundance and activation of signalling lipids which, as a result promotes pro-oncogenic pathways that could lead to resistance against anti-cancer treatments.

3. Lipid-based post-translational modification of proteins in cancer

The understanding of the role of lipids in the modulation of cellular processes in cancer cells (with comparison to normal cells) is important to help identify potential cancer markers. Since post-translational modification of proteins is an important component in many key signalling components during oncogenic progression, they are a suitable candidate for cancer studies. Ongoing research has highlighted the importance of various post-translational modifications that contribute to oncogenesis, namely phosphorylation, glycosylation, ubiquitination, prenylation, methylation and acetylation [81]. A common involvement of lipids in post-translational modification is known as prenylation. Prenylation is a process in which a hydrocarbon-based hydrophobic group (such as farnesyl [a 15-carbon isoprenoid] or geranylgeranyl) is covalently attached to a protein post-translation, which as a consequence changes cellular localization, protein-protein interaction, and function of the modified protein [82]. Prenylation is crucial for membrane association and activation of GTPases such as Ras, Rho, cdc42, and GPCRs, all of which are important regulators of cancer [83, 84]. For instance, stimulation of Ras proteins is known to promote oncogenesis by regulating gene expression, cell cycle progression, survival and migration [85]. Inactivation of the retinoblastoma protein (a tumour suppressor protein) induced unregulated expression of farnesyl diphosphate synthase and prenyltransferases, subsequently increasing prenylation/activation of N-ras in retinoblastoma tumour and promoted senescence [86]. Furthermore, prenylation is also known to involve farnesyl-pyrophosphate, an intermediate for cholesterol synthesis. Given the importance of lipid-based post-translational modification of proteins, many anti-cancer therapies currently target proteins and enzymes of the prenylation pathway [87, 88].

Another type of lipid-related post-translational modification is termed acylation, which is the process of adding fatty acids to amino acids. Protein acylation is tightly regulated by histone acetyltransferases (HATs) and deacetylases (HDACs), and modulates various cellular functions such as cell proliferation, differentiation, and migration [89]. HATs have been reported to modulate cancer in two ways depending on the site of acetylation and type of cancer-one pro-tumorigenic and the other tumour-suppressive [90]. For instance, histone hyperacetylation was reported in liver cancer cells [91] whereas deficiency in acetylation was observed in prostate cancer patients [92]. In gastrointestinal carcinomas, decreased histone acetylation is significantly associated with severity of tumour invasion and metastasis [93]. Moreover, Kang and colleagues [94] demonstrated that curcumin-induced histone hypoacetylation triggers caspase-3-dependent apoptosis and promotes neuron differentiation of neural progenitor cells in brain cancer. The role of HDACs in cancer was also demonstrated in several cancers such as cervical [95], colon [96], and gastric cancer [97]. Similar to HATs, HDACs also have a dual function in cancer regulation. For example, loss of HDAC1 in teratomas increased apoptosis and induced cell arrest, albeit no change in tumour size [98]. Similarly, increase in cellular differentiation and apoptosis was observed when HDAC2 expression was ablated in colorectal cancer cells [95]. In contrast, knockdown of HDAC6 promoted migration and tube formation in HUVEC cells *in vitro* [99].

The modification of proteins by lipids is also important for cellular localization and transport [100]. For example, attachment of GPI to proteins triggers translocation to the outer leaflet of the plasma membrane, which is important for signal transduction events [101]. Therefore, the knowledge of different types of lipid-based post-translational modification of proteins is useful to dissect the causal effects of these modifications in the context of cancer biology.

4. Lipids and autophagy in cancer

The recycling and circulation of lipids within a cell is regulated by lysosomes, a membrane enclosed organelle containing hydrolytic enzymes [102]. In recent years, there have been emerging studies indicating the importance of lysosomal-mediated degradation, a process termed autophagy, in maintaining cellular lipid homeostasis in various tissues [103]. Autophagy is essential for cell survival in the event of nutrient deprivation, where intracellular proteins and organelles are targeted to the lysosome for degradation as an alternative source of recycled energy [104]. There are three commonly described autophagy processes: autophagy (also referred as macroautophagy) [105], microautophagy [106], and chaperone-mediated autophagy [107]. Dysregulation in autophagy is associated with a wide array of diseases such as metabolic, cardiovascular, and neurodegenerative diseases, ageing and cancer [108]. In addition to its role in starvation responses, growth and differentiation, and the clearance of dysfunctional/damaged cytoplasmic protein and organelles, autophagy has also been reported in tumour regulation in cancer [109].

The relationship between lipids and autophagy is of particular interest as autophagy has been widely established to have a role in cancer, albeit a complicated one. Some reports have stated that early in tumorigenesis, autophagy may act as a tumour suppressor mechanism (reviewed in [110, 111]). Beclin-1, the mammalian ortholog of yeast autophagy-related gene 6 (Atg6), has been widely accepted as a candidate for tumour suppression. Allelic deletion of Beclin-1 [112] and reduced protein expression [113] was observed in ovarian, breast, and prostate cancers. Beclin $1^{+/-}$ heterozygous mutant mice had reduced autophagic activity and spontaneous tumour development [114], indicating the importance of Beclin-1 in the causal effect of autophagy and tumour growth. However, as cancer progresses, autophagy becomes essential to overcome oxidative and metabolic stressors in the cell, hence improving cancer cell survival and progression [115]. For example, human cancer cells expressing the Ras oncogene are able to upregulate autophagy to support tumorigenesis and tumour cell survival under starvation conditions [116]. As autophagy can facilitate or suppress the development of cancer, targeting this facet as a cancer therapy should focus on both the regulation and inhibition of autophagy at the appropriate stages. It still nevertheless holds potential as a primary target or co-target as multiple studies have shown that inhibition of autophagy enhanced therapeutic effects against cancer in myeloma, breast, colon, and prostate cancer [117].

Lipids and lipid enzymes have indispensable roles in the autophagic process and can influence autophagy at various stages [118, 119]. For instance, the mTOR complex is an important negative regulator of autophagy and lipids such as phosphatidylinositol 3-phosphate (PI3P), diacylglycerol, and phosphatidic acids interfere with mTOR downstream signalling by acting independently to promote autophagy [118, 120]. During later stages of autophagy, cellular materials targeted for degradation are signalled to autophagosomes. Lipid droplets and the lipid enzyme phospholipase D have been postulated to regulate autophagosomes biogenesis as well as positively modulate autophagy *in vivo* and *in vitro* [121, 122]. Furthermore, Seo and

colleagues shown that upon starvation, SREBPs can directly activate genes related to autophagy and are required for autophagosome formation and association with lipid droplets.

5. Lipids in angiogenesis and lymphangiogenesis

Classic characteristics of malignant tumours are their augmented proliferative and invasive properties. In order for cancer cells to sustain these enhanced growth requirements as well as expansion into other tissues, they have been shown to induce angiogenesis for oxygen and nutrient supply [123]. Tumour vasculature is also useful for the clearance of metabolic end products such as lactic acid whose accumulation may be toxic to the tumour cells. New capillary formation into tumours can be stimulated by growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF) [124, 125]. In normal healthy cells, VEGF functions by creating new blood vessels during embryonic development and wound healing [126]. The tumour microenvironment is made up of a variety of cell types that are normal or quiescent. As a tumour expands in size, nutrient deprivation and hypoxia occurs. This triggers the production of VEGF and cytokines by the tumour into its surrounding microenvironment [127], thereby initiating the proliferation of endothelial cells which allows tumours to develop and grow exponentially. Although this vasculature initiation may provide the tumour with more oxygen and nutrients, the eventual outcome is not ideal. VEGF-induced formation of tumour vasculature are irregularly shaped, leaky, and often functionally abnormal [124]. The leaky nature of these tumour vasculature triggers the recruitment of platelets, which subsequently releases angiogenic stimulatory factors into the microenvironment to further promote angiogenesis [128]. Other than dissemination through blood vessels, tumour cells can also exploit the lymphatic vessel pathway for invasion into other tissues, hence promoting metastasis [129]. In particular, VEGF-C is the main mediator of lymphangiogenesis and lymph node metastasis [130].

The importance of lipids in tumour angiogenesis is highlighted in studies related to the bioactive sphingolipid derivative S1P. The function of S1P is comparable to growth factors VEGF and bFGF, where its secretion stimulates angiogenesis [131] and vascular maturation [132]. Interactions between S1P and these proangiogenic growth factors have also been reported and may provide a collective effect in promoting development of the vascular network [133]. S1P expression is upregulated in various tumours such as lung [134] and colorectal cancer [135]. Cancer cells are able to secrete S1P into their microenvironment to induce both angiogenesis and lymphangiogenesis [136, 137]; via binding of S1P receptors [138], thereby facilitating tumour spread. Furthermore, *in vitro* analysis revealed that high levels of S1P are associated with increased migration and tube formation in co-cultured vascular or lymphatic endothelial cells [139]. Angiogenic and lymphatic metastasis is also stimulated by the secretion of prostaglandins, a group of lipid compounds enzymatically derived from fatty acids [140]. In particular, PGE(2) in breast cancer is able to bind GPCRs and induce angiogenic regulatory genes for proliferation, tube formation and subsequently metastasis [141]. This was also true in prostate cancer where PGE(2) activates angiogenesis via the prostanoids EP2 and EP4 pathways to increase production of urokinase-type plasminogen and vascular endothelial growth factors to alter prostate cancer cell motility [142].

Lipid metabolism has also been implicated in angiogenesis. SREBP1 expression is elevated in newly formed vasculature [143]. In response to VEGF signals, endothelial cells activate SREBP1 and SREBP2 to trigger proliferation, migration,

and vascular formation [144]. Vice versa, inhibition of SREBP1 resulted in reduced production of pro-angiogenic factors [143]. Metastasis is one of the main causes of mortality in human cancers. Since angiogenesis and lymphangiogenesis provide a platform for tumours to acquire nutrients and metastasise, understanding the role of lipids in endothelial cell metabolism may be useful as a target for cancer therapy and drug resistance [145, 146].

6. Concluding remarks

Lipid metabolism and signalling are now widely accepted as major players in cancer biology. Targeting components such as enzymes, bioactive lipids, and receptors, all of which are important for maintaining lipid homeostasis, metabolism and signalling, have been shown to reduce cancer cell proliferation and metastasis. This can be achieved through various means such as modifying the function of enzymes involved in biosynthesis and metabolism of lipids, altering the structure, composition and localisation of bioactive lipids and lipid rafts, or through disruption of lipid-mediated tumour-stromal crosstalk in the tumour microenvironment, and by promoting apoptosis of cancer cells. Considering the central role of lipids in cancer, these strategies are encouraging for the treatment and cure against cancer.

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