

Review

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Review

Regulation of Autophagy via Carbohydrate and Lipid Metabolism in Cancer

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Simple Summary: Metabolism of carbohydrates and lipids are essential to meet different needs of cells. Another cellular pathway that is central for normal function of cells is the ability of our cells to target and degrade damaged organelles, misfolded proteins, etc. Autophagy provides cells with necessary energy as an end product. Cancer cells have high rate of proliferation and thus require more energy compared to normal cells. Not surprisingly, cancer cells highly depend on these metabolic pathways. This review provides an in-depth review of recent research findings on how carbohydrate and lipid metabolism regulate autophagy and how this impacts cancer cells.

Abstract: Metabolic changes are an important component of tumor cell progression. Tumor cells adapt to environmental stresses via changes to carbohydrate and lipid metabolism. Autophagy, a physiological process in mammalian cells that digests damaged organelles and misfolded proteins via lysosomal degradation is closely associated with metabolism in mammalian cells acting as a meter of cellular ATP levels. In this review, we discuss the changes in glycolytic and lipid biosynthetic pathways in mammalian cells and their impact on carcinogenesis via the autophagy pathway. Also, we discuss the impact of these metabolic pathways on autophagy in lung cancer.

Keywords: lung cancer; lipid metabolism; glucose metabolism; Krebs cycle; cholesterol metabolism

1. Introduction

Autophagy is a highly regulated process and generally classified into three major types: Macroautophagy, Microautophagy and Chaperone-Mediated Autophagy (CMA) (**Figure 1A**) [6–8]. Macroautophagy (thereafter autophagy) involves the formation of double membrane structures

called autophagosomes, which engulf cargoes such as misfolded proteins, cytoplasmic proteins, or damaged organelles within the cell.

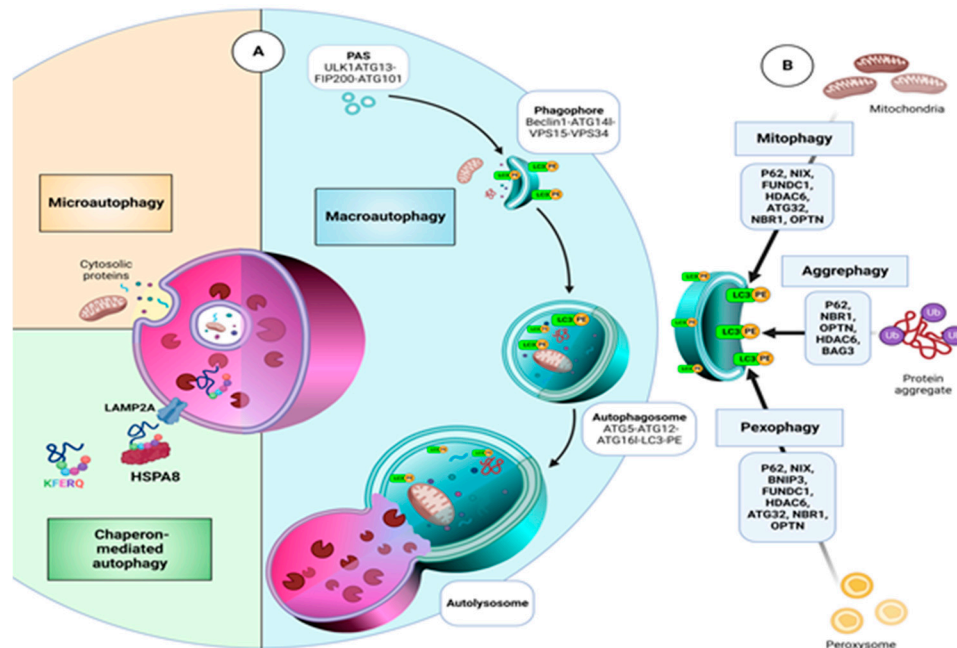


Figure 1. Autophagy is a self-eating mechanism occurring in cells. A) Different steps in the autophagy pathway. Cargos are first engulfed by autophagosomes, which then fuse with lysosomes. Lysosomal enzymes degrade the cargo resulting in the recycling of cargo's building blocks. B) Selective autophagy. Autophagy can selectively target and degrade specific cargo using different receptor proteins.

The autophagosomes then fuse with lysosomes, which contain hydrolases, resulting in the degradation and recycling of cargo contents [9–11]. Microautophagy is the direct fusion of cargo with lysosomes. During microautophagy, lysosomal or endosomal membranes are invaginated followed by the fusion of cargo with these organelles and finally their degradation and recycling [13]. CMA is a very selective type of autophagy. CMA is distinct from macroautophagy and microautophagy in that it does not require membranes for the engulfment of the cargo. CMA selectively targets proteins which contain a specific KFERQ pentapeptide residue (Lys-Phe-Glu-Arg-Gln). This residue is detected by cytosolic heat shock cognate 70 KDa protein (hsc70). The target protein and hsc70 complex are transported into the lysosome by the lysosomal-associated membrane protein 2A (LAMP2A) receptor in the lysosomal membrane [14,15]. Autophagy can also be selective in detecting cargoes using specific mediators. Therefore, this has resulted in new terminologies such as pexophagy (for peroxisomes), mitophagy (for mitochondria), and aggrephagy (for aggregates) [16,17] (Figure 1B).

Autophagy protects cells from stress caused by DNA damage, reactive oxygen species (ROS), adenosine triphosphate (ATP) deficiency, and nutrient deprivation [18–22]. In normal cells, autophagy occurs at a basal level whereas it significantly increases in cancer cells to support their high metabolic energy demands [23–26].

Autophagy is tightly regulated via different mechanisms. These include the processing of autophagy-related gene (ATG) proteins, the ULK1 kinase complex (ULK1-mAtg13-FIP200-Atg101), the class III phosphatidylinositol 3-kinase (PI3K) complex, VPS34 complex, and the ATG5-ATG12-ATG16 complex interaction with light chain 3 (LC3)-II [20,27,28] (Figure 1A). Autophagy is usually a part of the response to chemotherapy agents in tumor cells and it can increase or decrease

chemotherapy-induced apoptosis [29,30]. This response is dependent on the type of tumour cells and chemotherapy agents used [30–34].

Autophagy plays a double-edged sword role in cancer-suppression and cancer-promotion [15]. In the cancer initiation stages, autophagy removes damaged organelles or misfolded proteins to suppress factors involved in cancer initiation (such as reactive oxygen species (ROS) and the unfolded protein response). Conversely, in late stages of cancer, autophagy may provide energy for cancer cell metabolism, facilitate tumor cell metastasis [35–38], or induce chemotherapy resistance [15,20,39].

Metabolism comprises all the biochemical reactions that living cells use to generate the energy required for cell development, survival, and proliferation. [40–43]. Glycolysis, the Krebs cycle (glucose metabolism), and lipid metabolism are responsible for providing the required energy and building blocks for living cells. Glycolysis occurs in both aerobic and anaerobic conditions. The steps of glycolysis pathway are summarized in **Figure 2A**. The Krebs cycle, also known as the citric acid cycle or the tricarboxylic acid (TCA) cycle, is summarized in **Figure 2B**. The interconnection of glycolysis and the TCA cycle is visualized in (**Figure 2A,B**). Fatty acids (FAs) are the most common form of stored energy, and triacylglycerols (TAGs) are the most common non-toxic form of FAs [44]. Generally, there are four sources to acquire FAs and TAGs: de novo lipogenesis (DNL), cytoplasmic TAG stores, FAs derived from TAGs of lipoprotein remnants taken up by the liver, and plasma non-esterified fatty acids (NEFA) released by adipose tissue [45]. The liver and adipose tissue are the two main sources in the body that produce FAs. FAs synthesized and exported from the liver provide an energy source and lipoprotein structural components for building cell membranes. FAs synthesized in adipose tissue through DNL contribute to long-term energy storage [46]. DNL is a metabolic pathway under tight regulation that involves a series of enzymatic reactions, occurring primarily in the liver and adipose tissue, to produce FAs from surplus carbohydrates to store energy. This pathway is summarized in **Figure 2C** [47–49].

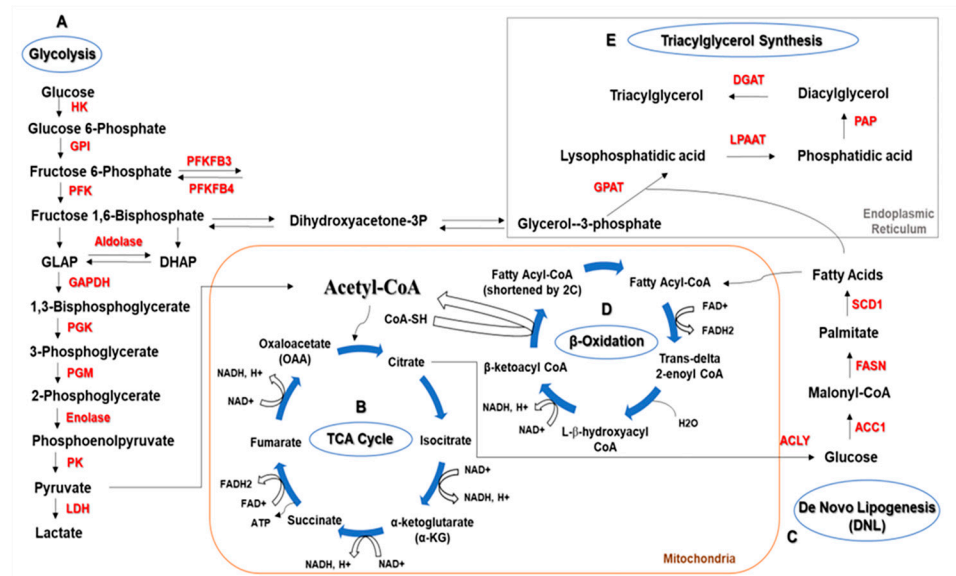


Figure 2. A) Glycolysis: It includes 10 consecutive enzymatic reactions in the conversion of glucose into two molecules of pyruvate, which connect with other metabolic pathways. Glucose is phosphorylated to glucose 6-phosphate by the enzyme hexokinase (HK). Glucose 6-phosphate is turned into fructose 6-phosphate by glucose phosphate isomerase (GPI). Phosphofructokinase-1 (PFK) catalyzes the conversion of fructose 6-phosphate and ATP to fructose 1,6-bisphosphate and ADP. 6-phosphofructo2-kinase/fructose 2,6-bisphosphatase (PFKFB), a family of bifunctional enzymes that control the levels of fructose 2,6-bisphosphate (PFKFB3 and PFKFB4 are the two main isoenzymes of this family) [PFK and PFKFB are two major regulatory enzymes in glycolysis [4]]. Subsequently, the aldolase enzyme catalyzes a reversible reaction in which fructose 1,6-bisphosphate converts into glyceraldehyde-3-phosphate (GLAP) and dihydroxyacetone phosphate (DHAP). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) produces 1,3-bisphosphoglycerate. Next, phosphoglycerate kinase (PGK) forms ATP and 3-phosphoglycerate. Phosphoglycerate mutase

(PGM) isomerizes 3-phosphoglycerate into 2-phosphoglycerate. Next enolase converts 2-phosphoglycerate to phosphoenolpyruvate which is phosphorylated to form a molecule of pyruvate and a molecule of ATP via pyruvate kinase (PK). Finally, lactate dehydrogenase (LDH) catalyzes the conversion of pyruvate to lactate. [5]. **B) Krebs cycle:** The TCA cycle starts with the combination of acetyl-CoA, generated from fatty acids, amino acids, or pyruvate oxidation, with oxaloacetate (OAA) to produce citrate. Citrate is converted into isocitrate. The cycle continues with two consecutive oxidative decarboxylations in which isocitrate is converted into the α -ketoglutarate (α -KG) and the succinyl-CoA concomitantly producing two CO₂ and two NADH. Succinyl-CoA converts into succinate, coupled with the release of ATP. Subsequently, fumarate is formed by the oxidation of succinate. During this step, two hydrogen atoms are transferred to FAD, producing 2FADH. Next, fumarate is converted into malate and further into OAA which combines with another acetyl-CoA, continuing the cycle [12]. **C) De novo lipogenesis C):** In this simplified scheme, pyruvate from glycolysis feeds acetyl-CoA to the TCA cycle. Citrate from the TCA cycle is converted to acetyl-CoA in the cytosol by ATP citrate lyase (ACLY). Acetyl-CoA from the TCA cycle and other sources is subsequently converted to complicated fatty acids by a series of enzymes including ATP-citrate lyase (ACLY), acetyl-CoA carboxylases 1 (ACC1), fatty acid synthase (FASN), stearoyl-CoA desaturase-1 (SCD1). **D) Fatty acid β -oxidation:** Each cycle leads to the formation of acetyl-CoA, nicotinamide adenine dinucleotide (NADH), and flavin adenine dinucleotide (FADH₂). The electron carriers NADH and FADH₂ are used by the mitochondrial respiratory chain to generate ATP. **E) Triacylglycerol synthesis:** This reaction occurs at the surface of the endoplasmic reticulum (ER) bilayer membrane. The first step in this pathway is the acylation of glycerol-3-phosphate by glycerol-3-phosphate acyltransferase (GPAT), producing lysophosphatidic acid. This is followed by further acylation by LPA acyltransferase (LPAAT) and dephosphorylation by phosphatidic acid phosphorylase (PAP) to yield diacylglycerol (DAG). The final step is converting 1,2-diacylglycerol into triacylglycerol (TAG), which is catalyzed by diacylglycerol acyltransferase (DGAT).

In the presence of oxygen, pyruvate is transported into mitochondria where it is converted into acetyl-CoA. In addition, many cells also utilize FA β -oxidation which involves breaking down a long-chain acyl-CoA molecule into acetyl-CoA molecules (summarized in **Figure 2D**) [50–54]. The other lipid metabolic pathway is triglyceride biosynthesis. They are synthesized by esterification of FAs into glycerol (summarized in **Figure 2E**) [46,55–57].

Compared to normal cells and apart from autophagy, cancer cells exhibit increased glucose uptake and lactate production even in the presence of oxygen [58]. This process of aerobic glycolysis was coined the “Warburg Effect” [58]. The Warburg Effect is of prominent importance in cancer cells for numerous reasons. It results in a higher rate of cytosolic ATP production compared with that in mitochondria. Therefore, aerobic glycolysis produces more ATP than oxidative phosphorylation (OXPHOS) per unit time [59].

Cells with this higher rate of ATP production gain a selective advantage when accessing shared and limited resources, such as the limited glucose in the cancer microenvironment [60]. When the demand for ATP is increased, aerobic glycolysis is rapidly increased, while OXPHOS remains constant [59,60]. The Warburg Effect also supports unregulated proliferation by feeding into biosynthesis. The increased glucose consumption serves as a carbon source for anabolic processes (e.g., lipid, nucleotide, and protein synthesis). The excess glucose also allows for a greater production of reducing equivalents of NADPH by the pentose phosphate pathway (PPP), which is needed for reductive biosynthesis [60]. It has been proposed that this inefficient way of ATP production is a trade-off for maintaining the high flux through anabolic pathways in cancer cells.

Lactate may be the only oncometabolite involved in all the hallmarks of cancer progression, and it has been suggested that lactate production may be one of the main purposes of the Warburg Effect [59,61]. Lactate excretion from cancer cells contributes to the production of an acidic cancer microenvironment conferring a growth and metastatic advantage to cancer cells [62]. The low extracellular pH (pHe) promotes mutagenesis, chromosomal abnormalities, and genome instability [63], allowing cells to acquire mutations that favor malignant progression. The low pH stimulates cancer cells to secrete proteins that will degrade the extracellular matrix (ECM) and promote

angiogenesis, creating an environment that favors intravasation, invasion, and metastasis [61,62]. The acidic microenvironment also represses lymphocytes, helping cancer cells with immune evasion [64]. This allows cancer cells to survive, metastasize, and colonize distant sites. Finally, lactate and the acidic microenvironment induce epithelial-to-mesenchymal transition (EMT) in cancer cells through the activation of autophagy and transforming growth factor β (TGF β) [37,38,65] expression, thus increasing motility and invasiveness and subsequently metastasis [66,67]. Several investigations have shown that suppression of glycolysis increases autophagy, which becomes a propelling force of OXPHOS for ATP production to support cancer cell survival [68–70]. Recent research has shown that glycolytic enzymes and metabolic intermediates of glycolysis are involved in autophagy regulation [68–70].

Reprogramming of lipid metabolism in cancer directly contributes to malignant transformation and progression [58]. The expression levels of some of the crucial enzymes in lipid metabolism are altered in cancer. For example, Fatty Acid Synthase (FASN), which is a multi-enzyme protein complex that catalyzes FA synthesis, is upregulated in cancer [60]. Sterol regulatory element-binding proteins (SREBPs) are a family of transcription factors regulating the expression of genes involved in the uptake and synthesis of FAs [67]. SREBPs are also upregulated in various cancers and promote cancer growth. It has been shown that the overexpression of lipid metabolism-related enzymes (e.g. FASN and SREBPs) is correlated with advanced stages of different type of cancers, poor patient survival, and cancer cell proliferation, invasion, and metastasis [71]. Moreover, the fatty acid oxidation (FAO) of lipids is increased in cancer cells to provide them with ATP to promote growth and survival under metabolic stress. In addition, FAO produces NADPH, which protects cancer cells from the oxidative stress of ROS [71]. Interestingly, different studies have recently shown the intricate link between autophagy and lipid homeostasis [72–74]. Autophagy plays a crucial role in the intracellular degradation of lipids [75–77]. This helps produce precursors required for the biosynthesis of other lipids, repair damaged structures, and produce energy necessary for anabolic processes within the cell that require lipid building blocks [58]. Lipids play a crucial role in autophagic activity in multiple tissues. Therefore, they have important implications for diseases like cancer [78,79]. The interconnection between lipid metabolism and autophagy is further highlighted by shared regulators, such as AMPK, mTORC1, TFEB, PPARs [80–82]. Similar to glycolysis, lipid metabolism can exert its effects on autophagy during cancer through both lipid metabolites and the enzymes involved in lipid metabolism.

In the current review article, we will discuss and explain how the different steps of glycolysis and lipid metabolism are connected to autophagy, and their impact on tumorigenesis and metastasis. In the last section, we will specifically focus our discussion on the impact of autophagy and these metabolic pathways in lung cancer.

2. Glycolysis and Autophagy Regulation in Cancer

In this section, we will discuss the key enzymes involved in regulating glycolysis and their effect on autophagy.

2.1. Hexokinase 2 (HK2)

HK2 catalyzes the initial step of glycolysis, which is the conversion of glucose to glucose 6-phosphate [83,84]. In mammals, there are four hexokinase isoforms: HK1, HK2, HK3, and HK4 [85]. Among the subtypes, HK2 is considered the most important one, which is overexpressed in various tumors including breast, lung, gastric and laryngeal squamous cancer, hepatocellular carcinoma (HCC), and renal cell carcinoma [86–93]. In addition to its critical role in glycolysis and autophagy, HK2 also facilitates apoptosis resistance and the induction of chemo-resistance in pancreatic, epithelial ovarian and breast cancers by increasing its expression or dimerization and interaction with voltage-dependent anion channels [94–98]. HK2 is overexpressed in ErbB2-driven breast cancer for tumor initiation and maintenance [99]. Further studies have shown that targeting HK2 via miR-143 inhibited cell proliferation and the Warburg Effect in colon [100], breast [101], prostate [102], and

renal cell cancers [92]. Overall, overexpression of HK2 results in an enhanced autophagic response. In contrast, suppression of autophagy is seen with inhibition of HK2 (**Figure 3A**) [103].

2.2. Phosphofructo-Kinase/Fructose Biphosphatases (PFKFBs)

PFKFB controls the intracellular steady-state concentration of fructose 2,6-bisphosphate (F2,6P2) [104]. There are four isozymes of PFKFB (PFKFB1–4), which display different properties, including tissue specific expression and response to kinases and phosphatases [105,106]. PFKFB3 and PFKFB4 are found overexpressed in breast [103,107–113], bladder [114,115], pancreatic [116,117], and gastric cancers [116,117]. Mechanistically, low levels of ATP leads to the phosphorylation of the C-terminal domain at Ser461 of PFKFB3 by the cellular energy sensor AMPK [118]. In addition, this condition induces MK2 [MAPK (mitogen-activated protein kinase)-activated protein kinase 2] phosphorylation at Thr334 via p38 α MAPK, which in turn activates PFKFB3 (phosphorylation at Ser461). Moreover, MK2 also activates SRE (serum-response element) in the promoter region of the PFKFB3 gene via phosphorylation of SRF (serum response factor) at Ser103, resulting in increased transcription and activity of PFKFB3, to amplified glycolytic and autophagic rates (**Figure 3B**) [118]. Klarer et al. demonstrated that inhibition of PFKFB3 using either siRNA transfection or derivatives of a PFKFB3 inhibitor, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO), initiates survival autophagy in HCT-116 colon adenocarcinoma cells [119]. Some studies showed that PFKFB4 depletion promoted oxidative stress, ultimately triggering survival autophagy as a stress-adaptive survival mechanism in the lung cancer [120,121].

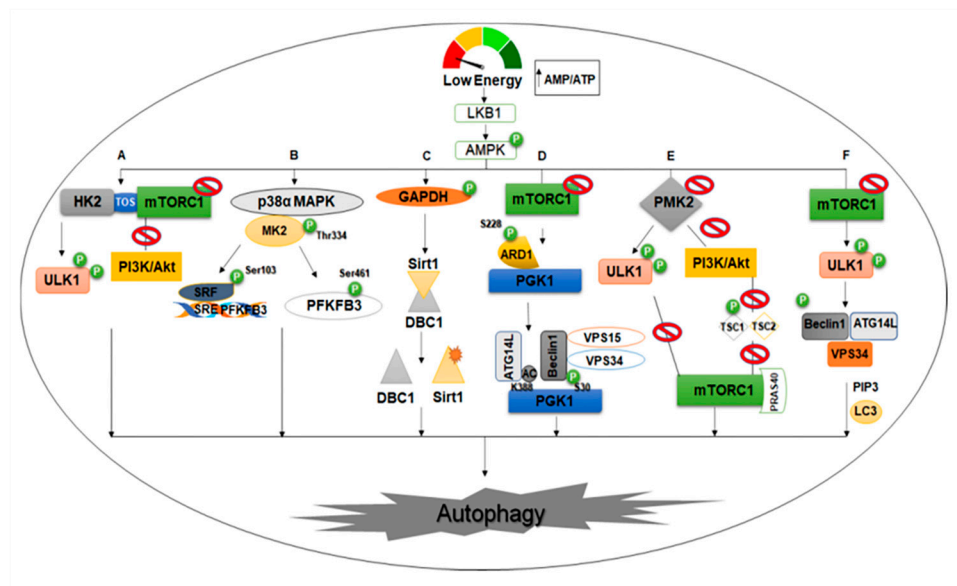


Figure 3. Autophagy is regulated by multiple signaling pathways which creates a complex interaction system. The glycolysis-related enzymes and glycolysis metabolic intermediates (A-F) are involved in the regulation of autophagy acting as a double-edged sword to sustain cancer cell survival under conditions of energy shortage.

2.3. Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH)

GAPDH catalyzes the conversion of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate in glycolysis, which is a reversible reaction [122,123]. As well as playing the vital role of maintaining aerobic glycolysis in the cytosol, GAPDH also participates in several non-glycolytic functions including autophagy [124]. In the cytosol, under glucose shortage, GAPDH is phosphorylated at Ser122 by AMPK. This leads to GAPDH redistributing into the nucleus, where it interacts directly with sirtuin1 (SIRT1) to stimulate SIRT1 activation and autophagy, increasing SIRT1 deacetylase activity and disassociating its inhibitor DBC1 (deleted in breast cancer-1) (**Figure 3C**) [125]. In general, various studies have shown that the GAPDH overexpression is associated with breast, ovarian, lung, and prostate cancers aggressiveness and metastases [122,126–130]. Therefore, GAPDH depletion is

recommended as a novel strategy to control tumor cells. GAPDH inhibitor (3-bromo-isoxazoline) induces autophagy and inhibits the proliferation of pancreatic ductal-adenocarcinoma cells (PDAC) and pancreatic-cancer stem cells (CSCs) [131]. Furthermore, the ROS/Akt/mTOR axis is activated by the inhibition of mitochondrial uncoupling protein 2 (UCP2) in pancreatic adenocarcinoma cells, which in turn leads to tumor cell growth arrest, induction of caspase-mediated apoptosis and translocation of GAPDH into the nucleus to promote Beclin1-mediated autophagy [132].

2.4. Phosphoglycerate Kinase (PGK)

PGK coordinates ATP production in glycolysis by catalyzing the conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate. PGK has two isoforms: PGK1 and PGK2 [133,134]. PGK1 has a significant role in sustaining cellular homeostasis and autophagy, making it an attractive molecular target for cancer therapy. The condition of glutamine deprivation and hypoxia inhibit mTOR-mediated arrest-defective protein 1 (ARD1) Ser228 phosphorylation, leading to ARD1 binding to PGK1 and Lys388 acetylation with subsequent PGK1-mediated Beclin-1 Ser30 phosphorylation. This activates ATG14L-associated class III phosphatidylinositol 3-kinase VPS34 to initiate autophagosome formation in glioblastoma (GBM) patients. ARD1-dependent PGK1 acetylation and PGK1-mediated Beclin-1 Ser30 phosphorylation are involved in brain tumorigenesis [135] (**Figure 3D**). In another investigation it has been shown that PGK1 induced the phosphorylation of PRAS40 (proline-rich AKT substrate of 40 kDa, encoded by the gene AKT1S1) at Thr246 in Ewing's sarcoma cell line A673, and liver cancer cell lines HepG2 and SNU449. PRAS40 is involved in PGK1 induced cancer cell growth. It was found that PGK1 inhibits autophagy-mediated cell death, which is associated with PRAS40. In the normoxic conditions, PGK1 blocks autophagic cell death via PRAS40 phosphorylation stimulating cellular proliferation. In hypoxia, PGK1 interacts with BECLIN1 and induces its phosphorylation with subsequent autophagy induction. Therefore, PGK1 is potentially a novel autophagy modulator for tumorigenesis between repressing autophagy-mediated cell death via PRAS40 and inducing autophagy through BECLIN1 based on oxygen levels in the environment [136].

2.5. Pyruvate Kinase (PK)

PK catalyzes the conversion of phosphoenolpyruvate (PEP) to pyruvate, which is the final step of glycolysis. PK has four isoforms: PKL (liver), PKR (erythrocytes), PKM1 (muscle and brain), and PKM2 (brain and liver) [137–139]. PKM2 can be a tetramer or dimer and the tetramer form has a higher affinity for PEP, while the dimer has lower affinity. Under physiological conditions, the tetramer form dominates, whereas cancer cells primarily prefer the dimeric form, which is necessary for the Warburg Effect (aerobic glycolysis). In other words, the lower activity of the dimeric form of PKM2 induces an increase in glycolysis, and can promote tumor survival and growth [137,138,140–145]. Therefore, identifying new compounds as PKM2 activators could be a potential therapeutic strategy for cancer treatment.

Many investigations provide evidence that PKM2 is involved in autophagy. Overexpression of PKM2 leads to activation of class I PI3K that could lead to activation of the Akt-mTOR signaling pathway, which in turn inhibits autophagy. PKM2 phosphorylates PRAS40 and releases this protein from mTORC1 with its subsequent activation in pancreatic cancer (**Figure 3E**) [146]. Knockdown of PKM2 in cancer cells activates AMPK signaling to maintain energy homeostasis via autophagy activation in prostate cancer cells [140]. The downregulation of PKM2 acts as a tumor suppressor in acute myeloid leukemia (AML) by increasing BECLIN-1-mediated autophagy [147]. PKM2 is also overexpressed in HCC cells and is induced through the JAK/STAT3 pathway, which might be involved in the response of HCC tumor cells to chemotherapy-induced apoptosis [148].

2.6. Lactate Dehydrogenase (LDH)

LDH catalyzes the reduction of pyruvate to lactate with associated interconversion of NADH and NAD⁺. It has two isomers including LDHA and LDHB that support conversion of pyruvate to

lactate in cells and back, respectively. [149–151]. LDHA is enhanced in many types of cancers (lung, liver, testicular, and breast) to establish metabolic reprogramming. [152–156]. In tamoxifen resistant breast cancer cells, ATP production decreased in parallel with increased glycolytic pathway activity [157]. In this scenario, LDHA is associated to tamoxifen resistance via BECLIN1 induced pro-survival autophagy [157].

LDHB is a crucial contributor to lysosomal activity and basal autophagy in cancer. This enzyme converts lactate and NAD^+ to pyruvate, NADH and H^+ to create an acidic environment. This is essential for vesicle maturation and protease activation during autophagy, but the regulation of this has not yet been defined [158]. Liang Shi and et al. demonstrated that the protein sirtuin5 (SIRT5) caused hyperactivity of LDHB by deacetylation at Lys329 that triggered autophagy and accelerated growth of colorectal cancer cells (CRC). [146].

2.6. Lactate

One of the most important consequences of the Warburg Effect in cancer cells is the increase in lactate production, which in turn leads to the acidification of the tumor microenvironment, creating an extracellular pH ranging from 6.0 to 6.5 (**Figure 4**) [159,160].

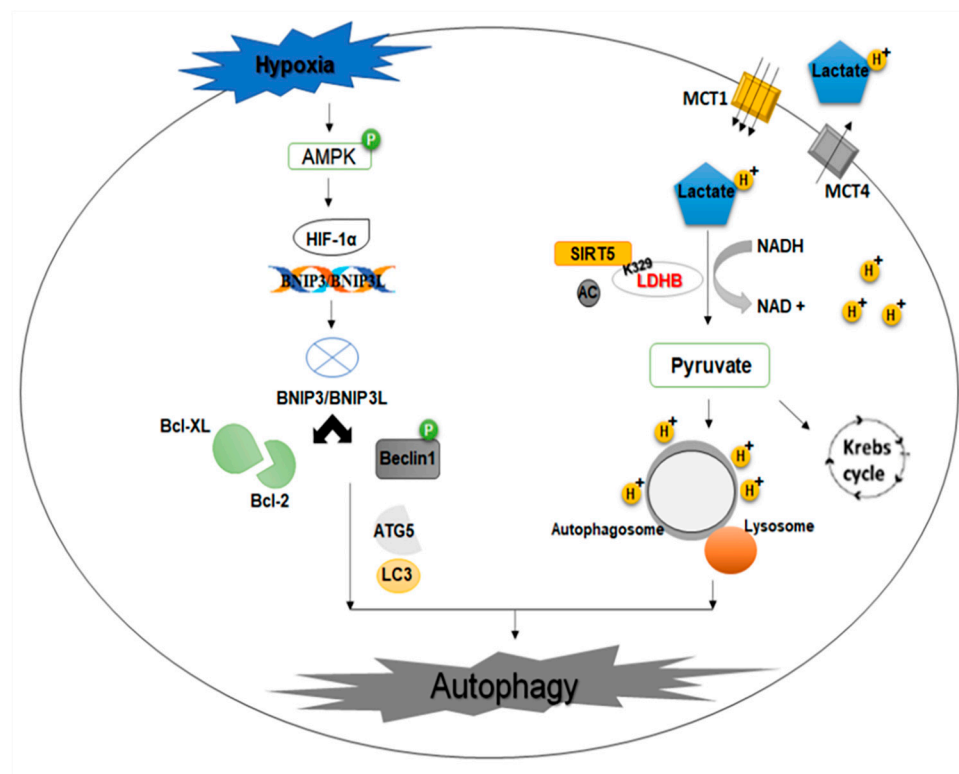


Figure 4. Hypoxia-induced autophagy (left): Hypoxic stress leads to the accumulation of HIF-1α. BNIP3 and BNIP3L, gene products targeted by HIF, are transcriptionally upregulated and compete with the Bcl-XL and Bcl-2 complex. This competition releases Beclin-1 from the complex, leading to the activation of autophagic machinery through the recruitment of several autophagic proteins including ATG5 and LC3. Acid-induced autophagy (right): Upon MCT1-mediated entry, lactate and NAD^+ are converted into pyruvate, NADH, and H^+ by LDHB. Then, protons generated by LDHB can promote lysosomal acidification and autophagy.

Emerging studies showed that lactate-induced acidosis leads to processes such as metastasis [161,162], angiogenesis [163–165], invasion [162,166], and immunosuppression [159,167]. Lactate itself cannot freely diffuse across the plasma membrane and monocarboxylate transporters 1-4 (MCT1-4) control the exchange of lactate across membranes [168,169]. Among MCTs, MCT1 and MCT4 are extensively expressed in cancer cell lines, playing an important role in metabolic

reprogramming and tumor aggression [170–174]. Regulating the expression of MCT1 via Osimertinib (OSI) activates liver kinase B1 (LKB1)/AMPK signaling, leading to autophagy induction in CRC cells [175]. On the other hand, blocking lactic acid export by inhibiting MCT4 provides an efficient anticancer strategy. MCT4 depletion by different doses of 7-aminocarboxycoumarin derivatives (7acc1) enhanced the cytotoxicity of NK cells in breast carcinoma by interfering with lactate flux, reversing the acidification of the tumor microenvironment, and inducing autophagy [176].

2.7. Hypoxia-Inducible Factor-1 (HIF-1) and Glycolysis

Adaptation to hypoxic conditions is achieved primarily through excessive accumulation of HIF-1 in tumor cells. HIF-1 increases the expression of the glycolysis pathway and compensates for the ATP demand of eukaryotic cells in the hypoxic condition [177]. Beyond its role in glycolysis, HIF-1 participates in autophagy by increasing the transcription of BNIP3 and BNIP3L genes which leads to the dissociation of the Bcl-XL and Bcl-2 complex and the activation of Beclin-1 induced autophagy [178,179] (**Figure 4**). Notably, glucose deprivation could induce HIF1-independent autophagy through induction of AMPK and inhibition of mTOR (**Figure 3F**). [180,181] The mTOR signaling pathway is inactivated under hypoxic conditions, leading to activation of ULK1, which is required for the initiation of autophagy (**Figure 3F**). Therefore, hypoxia-induced autophagy may be considered as a target to reverse the radio resistance in cancer cells. Yueming Shen and et al. showed that autophagy was inhibited by knockdown of lincRNA-p21. This occurred due to down-regulation of HIF-1 protein levels and activation Akt/mTOR/P70S6K signaling pathways. This is suggested a mechanism to enhance radiosensitivity of hypoxic tumor cells in human HCC and glioma cells [186]. A recent survey indicated that the expression of HIF-1 is commonly increased in a variety of human tumors, including lung, breast, and osteosarcoma [187].

We summarized the impact of the enzymes involved in glycolysis on autophagy in different cancers (excluding lung cancer which is discussed separately below) in **Table 1**.

Table 1. Glycolysis-related enzymes involved in the regulation of autophagy.

Enzyme Name	Enzyme Isoform	Type of Cancer	Molecules	Roles in Glycolysis and Autophagy	Ref.
PFKFBs	PFKFB3	Colon Adenocarcinoma	SiRNA & 3PO	Inhibit autophagy by knockdown of PFKFB3.	[119]
GAPDH	-	Pancreatic Adenocarcinoma	Genipin & Everolimus	Induce apoptosis and Beclin1-mediated autophagy.	[132]
PGK	PGK1	Breast Cancer	shRNA	Reduce the Warburg Effect.	[182]
PK	PKM2	AML	SiRNA	Reduce Beclin1-mediated autophagy.	[147]
		Gastric Cancer	miR-133b	Reduce glycolysis and autophagy by switching the PKM isoform expression	[183]

				from PKM2 to PKM1.	
LDH	LDHA	Breast Cancer	SiRNA	Regulate Beclin1-mediated autophagy.	[184]
	LDHB	Colorectal carcinoma	GW5074	Reduce autophagy by SIRT5 knockout or inhibition of LDHB acetylation at Lys329.	[185]
HIF	HIF-1	Human Liver & Glioma Cancer	shRNA- lincRNA-p21	Reduce glycolysis and inhibit autophagy by down-regulating HIF-1 protein.	[186]
		Cervical Cancer	SiRNA & 2-deoxyD-glucose or koningic acid	Inhibition of glycolysis and reduction of autophagy.	[68]
Lactate	-	Colorectal Carcinoma	Osimertinib	Induce autophagy by regulating the expression of MCT1 and activating LKB1/AMPK signaling.	[175]
		Breast Cancer	7acc1	Induce autophagy by the inhibition of MCT4	[176]

3. Lipid Metabolism and Regulation of Autophagy in Cancer

Historically, lipids have been challenging to study. However, through advancements in technology and methodologies have made it possible for progress in research on the role of lipids in autophagy and cancer progression. Despite recent discoveries about this relationship, our understanding of how lipid metabolism affects autophagy alterations during cancer is still rather limited. In this section, we aim to provide the most current findings and understanding of how changes in lipid metabolism influence autophagy during cancer. Lipids play a crucial role in autophagic activity in multiple tissues; therefore, they have important implications for diseases such as cancer [188,189]. The connection between lipid metabolism and autophagy is further strengthened by the common regulators that they both share including AMPK, mTORC1, Transcription Factor EB (TFEB), and PPARs [190–193]. Autophagy during cancer progression is modulated thorough lipid metabolism.

3.1. Enzymes in Lipid Metabolism Can Regulate Autophagy in Different Cancers

3.1.1. Fatty Acid Synthase (FASN)

FASN is an important cytoplasmic enzyme involved in fatty acid biosynthesis. The main function of FASN is to synthesize palmitate from acetyl-CoA and malonyl-CoA [194]. FASN expression increases the activation of mTOR, resulting in autophagy inhibition in leukemic blast cells obtained from AML patients [195]. Moreover, FASN can downregulate the expression of TFEB via mTOR. TFEB is phosphorylated by mTOR, leading to TFEB becoming localized in the cytoplasm and thereby inhibiting its transcriptional activity [195]. This can negatively affect autophagy induction since TFEB regulates the expression of genes involved in autophagy including lysosomal biogenesis, lysosomal membrane, lysosomal acidification, and other autophagy related genes [196]. This has been confirmed by the finding that inhibition of FASN promotes the nuclear translocation of TFEB where it can positively regulate the expression of lysosomal biogenesis genes such as LAMP1 [195]. Additionally, FASN has been found to self-modulate its expression via crosstalk with PI3K/Akt in clinical specimens of human osteosarcomas. It was found that overexpression of FASN has a positive relationship with the activation of PI3K-Akt in these clinical samples. In contrast, inhibition of FASN decreased Akt phosphorylation while Akt inhibition similarly inhibited the mRNA and protein expression of FASN in vitro [197]. In another study, it was found that FASN overexpression enhanced the cellular respiration (e.g., FAO) that favors cancer cells during CRC. In addition, FASN overexpression was correlated with less MAPK activation and accumulation of p62, indicating autophagy inhibition, which can favor the survival of CRC HCT116 and SW480 cells [198]. The overall effect of FAs in regulation of autophagy is summarized in (Figure 5).

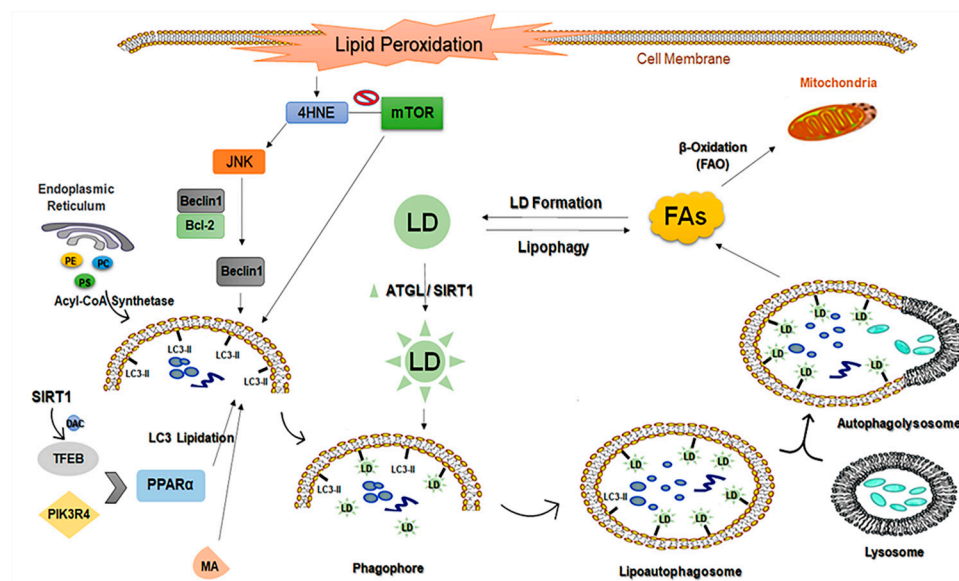


Figure 5. Crosstalk between lipids and autophagy. Lipids can modulate autophagy through different mechanisms.

3.1.2. 3-Hydroxy-3-MethylGlutaryl-CoA Reductase (HMGCR) Inhibitors

HMGCR is the rate limiting enzyme in the mevalonate pathway that synthesizes different lipids such as cholesterol, geranylgeranyl pyrophosphate (GGPP), and farnesyl pyrophosphate (FPP) [29,30,199,200]. Statins are a class of medications that inhibit HMGCR and thus decrease the de novo cholesterol levels [199,201,202]. Therefore, statins have been commonly used as cholesterol lowering agents. Statins have been shown to have pleiotropic effects that are independent of their cholesterol lowering properties [200]. However, inhibition of HMGCR by statins can affect the production of other downstream lipids that are produced in the mevalonate cascade. Changes in these lipids, in turn, can modulate autophagy and therefore affect cancer cell survival. It has been shown in human leukemia cells that blocking cholesterol biosynthesis using statins leads to autophagy induction via

inhibition of the Akt-mTOR pathway [203]. Interestingly, addition of cholesterol (but not GGPP or FPP) to cells attenuates the induced autophagy, indicating cholesterol dependent inhibition of autophagy in these cancer cells [204].

In HepG2 cells HMGCR inhibition by statins can induce autophagy through increasing LC3-II expression. Autophagy induction was confirmed after observing that statins further increased LC3-II expression when cells were also treated with Bafilomycin A1, an autophagy inhibitor [205]. Similar results were observed in atorvastatin-treated PC3 prostate cancer cells where a 10-fold increase in LC3-II expression was found.

This group observed that addition of GGPP, but not FPP, could reverse the atorvastatin induced autophagy. This indicated that autophagy induction by atorvastatin was due to inhibition of GGPP biosynthesis [206]. In human rhabdomyosarcoma cells depletion of GGPP with hydrophobic statins induced autophagy [207,208]. It was also shown that simvastatin inhibits the flux of autophagy in alveolar rhabdomyosarcoma cells through changing the acidity of lysosomes, which is different from C2C12 cells [209]. Statins (fluvastatin, lovastatin, simvastatin, and atorvastatin) can trigger the induction of autophagy in PC3 cells via inhibition of geranylgeranylation. Findings of this study suggested that autophagy induction by statins can potentially have a protective role against prostate cancer progression [206,210]. These findings highlight that lipid metabolites produced by the mevalonate pathway play a crucial role in autophagy regulation upon HMGCR inhibition in different types of cancer. Additionally, it has been shown in previous studies that combination therapy of statins with other anticancer agents can improve treatment response in different cancer cell lines (small-cell lung, ovarian and breast cancer, GBM, and acute myeloid leukemia) [30,211–214]. In agreement with these studies, we have previously shown that simvastatin prevents the fusion of autophagosomes and lysosomes in GBM cell lines thereby inhibiting autophagy flux. This autophagy flux inhibition potentiates the temozolomide-induced apoptosis in GBM cancer cells [30]. The impact cholesterol and the cholesterol biosynthesis pathway in regulation of autophagy is summarized in (Figure 6).

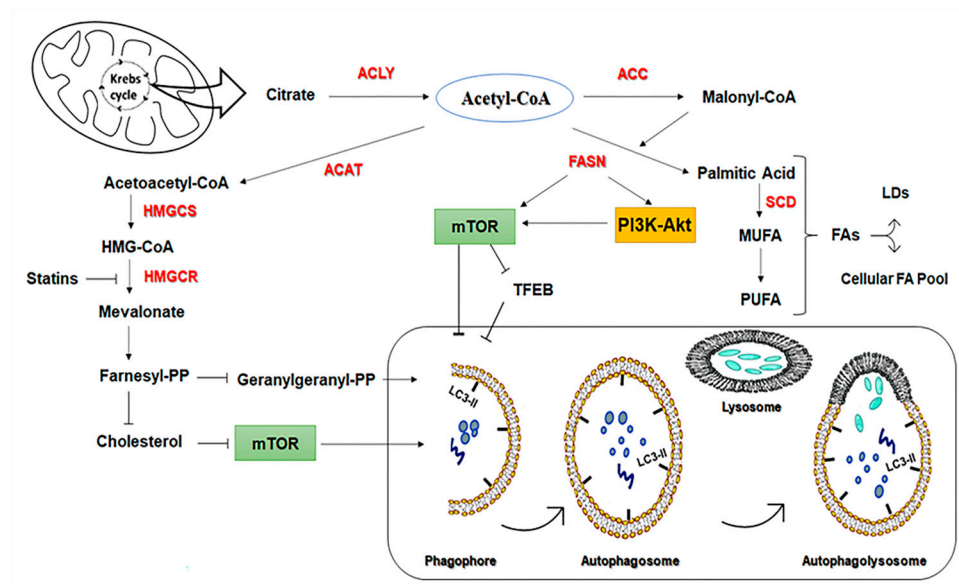


Figure 6. Mechanism of action of autophagy regulation upon HMGCR inhibition by statins. Also, the mechanism by which FASN can modulate autophagy during cancer is shown. ACLY: ATP citrate lyase, ACAT: acetyl-CoA acetyltransferase, HMGCS: 3-hydroxy-3-methylglutaryl-CoA synthase, HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase, ACC: acetyl-CoA carboxylase, FASN: fatty acid synthase, SCD: stearoyl-CoA desaturase, MUFA: monounsaturated fatty acid, PUFA: polyunsaturated fatty acid.

3.1.3. Sphingosine-1-Kinase (SPHK1)

SPHK1 is the enzyme that synthesizes sphingosine-1-phosphate (S1P) from sphingosine. It also plays a crucial role in maintaining the sphingolipid balance within the cell [215]. It has been shown that SPHK1 participates in the regulation of autophagy and in different aspects of malignancy including therapy resistance, cancer development, growth, and metastasis [216,217]. SPHK1 is highly expressed in different types of cancers, such as human astrocytoma, CRC, and prostate cancer. It has also been associated with angiogenesis and resistance to chemotherapy and radiotherapy [218–221].

Thus, SPHK1 has been proposed to serve as an oncogene in carcinogenesis [222]. Prior studies have found that SPHK1 plays a role in the biogenesis of autophagosomes by modulating the expression levels of LC3 and therefore autophagy in neuroblastoma cells. However, the exact mechanisms by which SPHK1 regulates autophagy in these cancer cells is yet to be elucidated [223]. Another study found that in breast cancer MCF-7 cells, SPHK1 induces autophagy by increasing the formation of LC3-positive autophagosomes thereby protecting them during nutrient deprivation [224]. SPHK1 also induces autophagy in CRC HT-29 cells via activation of SPHK1/ERK/pERK, which leads to the inhibition of mTOR and consequently ULK1 activation. SPHK1 was also shown to increase the expression of ATG5, ULK1, and LC3 in CRC HT-29 cells. Furthermore, autophagy has been linked to the survival of CRC cells during chemotherapy stress and is a marker of an invasive phenotype. Therefore, autophagy inhibitors such as Bafilomycin A1 and Chloroquine are suggested as promising interventions for CRC treatment [225]. Moreover, SPHK1 has been shown to induce EMT and consequently contribute to invasion and metastasis in HCC HepG2 cells [226]. This study revealed that SPHK1 induced EMT through enhancing lysosomal degradation of E-cadherin, a protein critical in epithelial cell-cell adhesion. Furthermore, this group found that S1P could stimulate the binding of TRAF2 (TNF Receptor Associated Factor 2) to Beclin1. TRAF2 binding catalyzes the ubiquitination of Beclin1 and therefore induction of autophagy. Overall, the authors concluded that the SPHK1-E-cadherin-TRAF2-Beclin1 pathway is responsible for EMT induction and subsequent metastasis in HCC cells. Thus, SPHK1 inhibition is proposed to decrease autophagy activation and is a possible strategy for

HCC treatment. SPHK1 also modulates autophagy in human peritoneal mesothelial cells (HPMCs) and plays a role in the progression of gastric cancer peritoneal dissemination (GCPD) [227]. SPHK1 expression was directly related to LC3 expression in 120 human samples from gastric cancer peritoneal tissue. The SPHK1-induced autophagy in HPMCs increased the invasive capability of gastric cancer cells whereas SPHK1 knockdown inhibited autophagy. This was associated with poor prognosis and recurrence in these patients. SPHK1 is also involved in the production of ceramide, a prominent lipid metabolite that will be discussed in the following section. Additionally, SPHK1 has an inhibitory effect on mTOR and therefore activation of autophagy independent of Akt [78]. The connection of sphingomyelin, ceramide, and SPHK1 to autophagy is summarized in **(Figure 7)**.

3.1.4. Fatty Acid Translocase/Cluster of Differentiation 36 (FAT/CD36)

FAT/CD36 is an enzyme localized within the cell membrane and is responsible for long-chain fatty acid uptake into the cell [228]. A study found that FAT overexpression inhibits autophagy in HCC HepG2 and Huh7 cells [229]. Consistent with these findings, they found that FAT knockdown induces autophagy in these cells as shown by increased formation of autophagosomes, LC3-II expression, and p62 degradation. FAT modulates autophagy through phosphorylation of Beclin1 and ULK1, acting as a negative regulator of autophagy in HCC cells [229]. In this same study, *in vivo* studies in mice with FAT knockout also showed elevated autophagy. This was further confirmed by the observation that autophagy was decreased after reconstituting FAT expression in FAT knockdown mice. Additionally, FAT knockdown caused an increase in lipophagy levels together with enhanced FA β -oxidation. These findings highlight that modulation of FAT expression could be a promising way to induce lipophagy in HCC cells, thereby mitigating the excessive lipid accumulation. **(Figure 7)**.

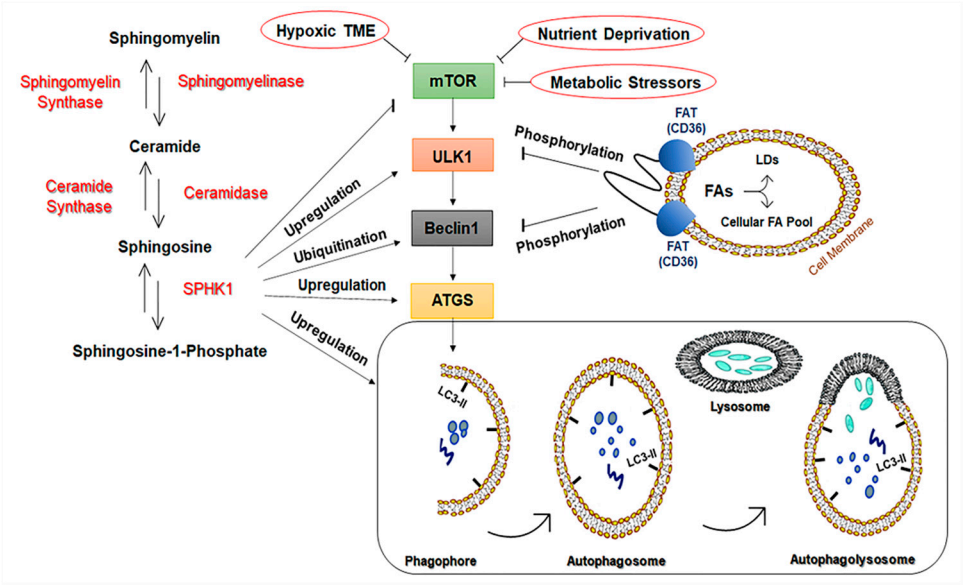


Figure 7. SPHK1 and FAT can regulate autophagy during cancer. A simplified scheme of sphingolipid metabolism and turnover is also shown.

We have summarized the effect of enzymes involved in lipid metabolism on different steps of autophagy in **Table 2**.

Table 2.

Enzyme	Function	Effect on autophagy		Cancer type	Ref
Fatty Acid Synthase (FASN)	Synthesizes palmitate from acetyl-CoA and malonyl-CoA	a)Activation of mTOR and subsequent downregulation of TFEB	Inhibition	Acute Myeloid Leukemia	[195]
		b)Activation of PI3K-Akt	Inhibition	Osteosarcoma	[197]
		c)MAPK inactivation	Inhibition	Colorectal Cancer	[198]
3-Hydroxy-3-MethylGlutaryl-CoA Reductase (HMGCR)	Synthesizes cholesterol, geranylgeranyl pyrophosphate and farnesyl pyrophosphate, etc	a)Cholesterol-dependent inhibition of Akt-mTOR upon HMGCR inhibition by Lovastatin	Induction	Acute Lymphocytic Leukemia	[203]
		b)Geranylgeranyl pyrophosphate-dependent upregulation of LC3-II upon HMGCR inhibition by Atorvastatin	Induction	Prostate Cancer, Rhabdomyosarcoma	[206]

Sphingosine-1-Kinase (SPHK1)	Synthesizes sphingosine 1 phosphate (S1P) from sphingosine	a) Promotes biogenesis of autophagosomes by modulating the expression levels of LC3	Induction	Neuroblastoma	[223]
		b) Increasing the formation of LC3-positive autophagosomes	Induction	Breast Cancer	[224]
		c) Activation of the SphK1/ERK/p ERK leading to the inactivation of mTOR, elevated expression of ATG5 and ULK1	Induction	Colon Cancer	[225]
		d) Enhancing the lysosomal degradation, increasing the ubiquitination of Beclin1	Induction	Hepatocellular Carcinoma	[226]
		e) Upregulation of LC3 expression	Induction	Gastric Cancer	[227]
Fatty Acid Translocase (FAT/CD36)	Long-chain fatty acid uptake	a) Phosphorylation of Beclin1 and ULK1	Inhibition	Hepatocellular Carcinoma	[229]

3.2. Lipid Metabolites Can Regulate Autophagy in Different Cancers

3.2.1. Phosphatidic Acid (PA)

PA is produced through the breakdown of phosphatidylcholine into PA and choline by Phospholipase D [230]. Although different targets for PA have been reported, the most significant target of PA in cancer cells is likely to be mTOR [231]. PA regulates autophagy through mediating the induction of autophagy by inducing autophagosome curvature and inhibiting mTOR [232]. Furthermore, PA can be produced under nutrient and oxygen deprivation, which is common in human tumor sites [231]. Other metabolites of PA can also regulate autophagy. For example, Phosphatidic Acid Phosphatases can convert PA into diacylglycerol that has been shown to regulate autophagy [233]. Diacylglycerol induces autophagy through activation of PKC. It also helps dissociate BCL2 from Beclin1 through activation of JNK and thus initiates autophagy induction [233]. Lysophosphatidic acid (LPA) activates mTORC1 and decreases autophagy via phosphorylation of S6K and ULK in prostate cancer cells (PC3, LNCaP, and Du145 cells) [234]. It has been recently shown that HS1BP3 protein negatively regulates autophagosome formation in moderately differentiated osteosarcoma cells (moderately differentiated sarcoma) through phospholipase D (PLD) and PA production and increased localization of PLD1 to ATG16L1-positive membranes [235].

3.2.2. Sphingolipids

Another class of lipids are sphingolipids that play a prominent role in autophagy regulation as well as cell proliferation and differentiation [236]. Sphingolipids are a very important group of lipids that can regulate a wide range of crucial functions in cancer cells, such as cell growth and proliferation [237]. In particular, two sphingolipids have appeared to significantly regulate autophagy: ceramide and S1P. Ceramide can inhibit Akt which consequently inhibits mTOR, inducing autophagy. It has also been found that both ceramide and S1P can upregulate the transcription of Beclin1 and cause autophagy induction [238]. The product of ceramide hydrolysis is sphingosine which produces S1P via phosphorylation by SPHK1 [239]. Recent studies have shown that SPHK1 is activated under starvation conditions which consequently forms S1P [224]. Ceramide synthase 2 (CerS2) is one of six mammalian isoforms of ceramide synthase that can synthesize ceramide. It was shown that overexpression of CerS2 causes accumulation of ceramides, resulting in growth arrest and autophagy induction in SMS-KCNR neuroblastoma and MCF-7 breast cancer cells [237]. Additionally, it has been shown that treatment of HT-29 CRC cells with ceramide induces autophagy in these cells through elevating the pool of ceramides [240–242]. It was shown in MCF-7 breast cancer cells that ceramides increased the expression of Beclin1 and therefore induced autophagy [241]. Also, it has been shown that short-chain ceramides (C(2)-ceramide and C(6)-ceramide) and tamoxifen-induced stimulation of de novo ceramide synthesis causing the dissociation of BCL2 from Beclin1 and therefore induction of autophagy in Hela cells [238].

Sphingosine is generated from the hydrolysis of ceramide by ceramidase followed by its conversion to Sphingosine-1-Phosphate (S1P) by sphingosine kinases. S1P binds to its cell receptors and can modulate various cellular functions including proliferation, migration, and autophagy. It has been shown that elevated levels of intracellular S1P through overexpression of SPHK1 induces autophagy via inhibition of mTOR in human MCF-7 breast cancer cells [224,243]. Moreover, S1P can act as a survival mechanism in prostate cancer. It was shown that treatment with S1P in PC3 prostate cancer cells can induce autophagy through inhibition of mTOR [244]. It was concluded that S1P could mediate nutrient deprivation-induced autophagy as a survival mechanism during the early phase of prostate cancer development.

3.2.3. Peroxisome Proliferator-Activating Receptors (PPARs)

PPARs comprise a family of nuclear proteins including PPAR α , PPAR δ , and PPAR γ that serve as transcription factors, regulating the expression of different genes [245]. In order to be functional as a transcription factor, PPARs need to bind to lipid ligands through lipid-binding proteins [246]. These lipid ligands have been reported to be oleic acid, linoleic acids, linolenic acids, prostaglandins, eicosanoids, and oxidized lipids [247,248]. PPARs have been shown to regulate autophagy in different cancers via various pathways, such as regulation of autophagy-related genes [78]. Furthermore, TFEB is also activated following the activation of PPARs which upregulates the expression of different autophagy related genes, such as Rab7 and LAMP2 [249]. This finding has been further confirmed by the observation that mouse cells with PPAR δ knockout have a significant reduction in autophagy markers [250]. The levels of these lipid ligands change during cancer, which can directly influence PPARs and TFEB activation and thereby autophagy during cancer. For this reason, PPARs have been proposed as a promising treatment candidate for cancer. It has been found that treatment of Caco-2, a CRC cell line, with rosiglitazone (a PPAR δ agonist) induces autophagy [251]. Also, PPAR γ can activate PTEN, which is an inhibitor of PI3K. Upon PI3K inhibition, PIP3 production is reduced resulting in mTOR inhibition and induction of autophagy in CRC cells [251]. PPAR γ is active during cancer, and it has been suggested that PPAR γ activates autophagy in a self-sufficient manner. For example, PPAR γ has been shown to regulate autophagy in MDA-MB-231 breast cancer cells. It was shown that troglitazone (a PPAR γ agonist) induces autophagy in these cancer cells as shown by an increase in lysosomal acidification [252]. These findings, have instigated new proposals among cancer researchers that PPAR-induced autophagy benefits cancer cells by protecting them from metabolic stress and cancer therapy [252].

3.2.4. Free Fatty Acids (FFAs)

FFAs are byproducts of lipophagy, and they can regulate autophagy. The excessive accumulation of FFAs can result in cell death (known as lipotoxicity) [253]. Thus, the levels of FFAs are tightly regulated by lipophagy [254]. Palmitic acid is a common dietary FA [255]. A study on HCC cells showed that palmitic acid was able to induce autophagy flux independent of mTOR [256]. Human HCC HepG2 cells treated with palmitic acid showed activation of PKC and increased levels of diacylglycerol. As mentioned above, diacylglycerol can induce autophagy through activation of PKC and dissociation of BCL2 from Beclin1. Furthermore, PKC inhibition significantly reduced autophagy flux in these cells, confirming that palmitic acid induced autophagy flux through PKC [256].

3.2.5. Omega-3 PolyUnsaturated Fatty Acids (n-3 PUFAs)

n-3 PUFAs are involved in the modulation of autophagy [257]. Docosahexaenoic acid (DHA) is one of the most studied n-3 PUFAs [258]. DHA can be synthesized in the body in low amounts through the conversion of α -linolenic acid (ALA), which is a shorter chain omega-3 fatty acid [259] by elongase [260,261]. DHA has antitumor effects on various types of cancer through modulation of autophagy [262]. DHA has been studied in various cancers [263–265] and it exists in many phospholipids that form the cell membrane in different tissues [266]. In p53-wild type prostate cancer cell lines, it has been reported that DHA induces autophagy through AMPK activation resulting in the inhibition of mTOR [267]. In contrast, it induces autophagy through producing mitochondrial ROS in p53-mutant prostate cancer cells (PC3 and DU145). The generated ROS lead to the inhibition of Akt and mTOR and thus autophagy induction [268]. Interestingly, DHA alone or in combination with other chemotherapeutic agents can exert anticancer effects by boosting the immune response to cancer cells. It was found that DHA-induced autophagy increases the processing of cancer antigens. The subsequent cross-presentation of these cancer antigens to Antigen Presenting Cells (APCs) improve the immune response by ensuring the production of antitumor T cells [269]. DHA can also induce autophagy in CRC cell lines, Caco-2 and SW620 (by regulating the expression of genes involved in the autophagy process such as p62, LC3 and ATG14) [270], and HCC cell line, HepG2 (shown by accumulation of LC3-II and formation of LC3puncta) [271]. DHA exerts its anticancer effects in other cancer types such as GBM and cervical cancer [267] by induction of autophagy through mTOR inactivation.

DHA can be converted to docosahexaenoyl ethanolamine (DHEA) [272]. It has been shown that DHEA can activate autophagy in MCF-7 breast cancer cells [273]. It can increase the expression of PPAR γ , which can in turn upregulate PTEN. Finally, PTEN inhibits Akt-mTOR which subsequently induces autophagy. Moreover, in the same cell line, DHEA was able to phosphorylate BCL2, leading to its dissociation from Beclin1 and consequently inducing autophagy [273]. Although these promising findings highlight the potentiality of DHA and DHEA for anticancer treatment interventions, we will need more in vitro and in vivo studies to better examine their use in anticancer therapies.

3.2.6. Cholesterol

Cholesterol is mainly biosynthesized in the endoplasmic reticulum (ER) of hepatocytes. This process requires acetyl-CoA which is produced primarily during β -oxidation of FAs in the mitochondria [274]. Cholesterol is one of the major products synthesized by the mevalonate cascade and is necessary for the formation of cellular membranes, modulation of cell membrane fluidity, cellular structures, synthesis of hormones and vitamin D [275]. The rate limiting step in cholesterol biosynthesis is the conversion of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to mevalonate by HMG-CoA Reductase (HMGCR) [276] which is further processed into cholesterol and other lipid molecules such as GGPP, FPP, and squalene [277,278]. As discussed previously, the production of lipids including cholesterol can be inhibited by cholesterol lowering agents known as statins. Statins inhibit the rate limiting enzyme in this pathway, HMGCR [199].

The current knowledge of how cholesterol can modulate autophagy in the context of cancer is very limited. One study has shown that the inhibition of cholesterol biosynthesis by statins in blood cancer cells induces autophagy through inhibition of mTOR signaling [203]. Autophagy was also induced after treatment of these cells with methyl- β -cyclodextrin, a cholesterol reducing agent, indicating that autophagy induction by statins was due to cholesterol depletion. Cholesterol-mTORC1 axis regulated autophagy through Golgi membrane protein 1 (GOLM1) and interacting with LC3 through an LC3-interacting region (LIR) in hepatocellular cancer cells [280]. Cholesterol of the cytosolic membrane lipid raft regulated the autophagy cell death in breast cancer cell lines (MDM-MB231) via regulation of caspase-8 activity [281].

Table 3 shows the different lipid metabolites known to regulate autophagy in different types of cancer.

Table 3. Regulation of autophagy by lipid metabolites during cancer.

Lipid Metabolite	Effect on autophagy		Cancer type	Ref
Phosphatidic Acid	Induction of autophagosome curvature, inhibiting mTOR	Induction	Breast Cancer	[232]
Ceramide	Inhibition of Akt/mTOR, Upregulation of Beclin1 expression	Induction	Breast Cancer, Neuroblastoma	[237,241]
	Upregulation of Beclin1 expression	Induction	Colon Cancer	[241]
	Dissociation of BCL2 from Beclin1	Induction	Cervical Cancer	[240]
Sphingosine 1-phosphate (S1P)	mTOR inhibition	Induction	Prostate Cancer	[244]
	mTOR inhibition	Induction	Breast Cancer	[224,243]
Peroxisome Proliferator-Activating Receptors (PPARs)	PTEN activation, mTOR inhibition	Induction	Colorectal Cancer	[251]
	Increase in lysosomal acidification	Induction	Breast Cancer	[252]
Palmitic Acid	Activation of PKC, increasing the diacylglycerol levels	Induction	Hepatocarcinoma	[279]

Docosahexaenoic acid (DHA)	AMPK activation resulting in the inhibition of mTOR	Induction	p53-wild type prostate cancer	[267]
	Producing mitochondrial reactive oxygen species (ROS) resulting in Akt and mTOR inhibition	Induction	p53-mutant prostate cancer	[267]
	Upregulation of LC3 and ATG14 expression			
	mTOR inhibition		Colon Cancer	
	mTOR inhibition	Induction		[270]
		Induction	Glioblastoma	
		Induction	Cervix Carcinoma	[267]
		Induction		[267]
Docosahexaenoyl ethanolamine (DHEA)	Upregulation of PPAR γ which upregulates PTEN and consequently inhibits Akt-mTOR, and promotes BCL2 phosphorylation and therefore its dissociation from Beclin1	Induction	Breast Cancer	[273]
Cholesterol	mTOR inhibition	Induction	Acute Lymphocytic Leukemia, Chronic Lymphocytic Leukemia	[203]

4. Lung Cancer, Metabolism and Autophagy

Lung cancer is a major contributor to the global cancer burden. It is the second most diagnosed cancer in the world, only recently being surpassed by breast cancer in 2020 [282,283]. Globally, lung cancer accounts for 11.4% of all newly diagnosed cancers, representing 1 in 10 new cases [282,283]. It continues to be the number one cause of cancer related deaths worldwide, accounting for 1 in 5 cancer deaths in 2020 [284]. The death toll from lung cancer exceeds that of breast, prostate, and colorectal

cancer combined [282,284]. The five-year survival rate of lung cancer (18.4%) is lower than colorectal (64.5%), breast (89.6%) and prostate (98.2%) cancer [284]. 4 Metastasis, the dissemination of a primary tumor to other parts of the body, is the major cause of morbidity and mortality in lung cancer. Only 16% of cases of lung cancer are diagnosed at an early stage when the cancer is still localized to the lungs [284]. The five-year survival rate is only 5% for those with distant metastases, compared to 56% for those detected at an early stage [284]. Diagnosis at advanced stage contributes to the substantial mortality in lung cancer, with more than half of people dying of lung cancer within a year of their diagnosis [284].

In the following sections we will focus on the impact of metabolism and autophagy in pathogenesis of lung cancer.

4.1. Etiology, Pathogenesis, and Natural History of Lung Cancer

The majority of lung cancers are either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). NSCLC accounts for more than 80% of all lung cancers. Adenocarcinoma and squamous cell cancers are the most common subtypes of NSCLC [285]. Adenocarcinoma is currently the most common histologic subtype worldwide and histopathologically diagnosed through its specific morphology and immunohistochemical profile that includes the thyroid transcription factor-1 (TTF-1) and Napsin [286–288]. About 5-15% of Adenocarcinomas harbor targetable genetic driver mutations including EGFR, ALK and BRAF and KRAS. The signaling proteins in these genes drive proliferation of the malignant cells [289]. Programmed cell death-ligand 1, (PDL1) is a cell surface protein expressed in NSCLC patients; it is associated with poor prognosis and a therapeutic target for immune check point inhibitors [290–292].

Squamous cell carcinoma was previously the most common subtype but is now the second most common [286,293]. The majority of squamous cell carcinomas present as more central lung cancers (i.e., closer to the central bronchial tree). It is often defined by immunohistochemical staining for p40, p63, and CK5 or CK5/6 [286,294].

Although there is a combination of genetic and environmental risk factors for the development of lung cancer, the strongest risk factor is known to be environmental exposure to smoking [295]. Although there are growing populations of non-smoking individuals developing lung cancer, smoking is estimated to be a risk factor in 90% of patients who develop lung cancer [295]. Smoking exposure as a risk factor for developing lung cancer not only applies to people who smoke but also extends to second-hand smoke (involuntary inhalation of smoke by non-smokers) or third-hand smoke (exposure to smoke deposited on surfaces such as clothing, furniture, etc.) [296,297]. Although the data on third-hand smoke exposure is developing, there is established evidence that second-hand smoke exposure is associated with higher risk of developing lung cancer. The evidence suggests that there is a dose-response relationship between second-hand smoke exposure and the incidence of lung cancer among never-smokers [296,297]. For example, women who have never smoked had a 27% higher incidence of lung cancer if their spouse smoked [296].

A common established risk factor for lung cancer is exposure to radon [298,299]. Radon is a gas resulting from the decay of radium and uranium [298,299]. Due to its potential presence in soil and groundwater, it can potentially accumulate in homes [298,299]. Asbestos is also a known risk factor for lung cancer and appears to have a synergistic effect with smoking to increase risk of lung cancer [300,301]. Asbestos exposure can be due to occupational exposure or to exposure in homes or other buildings (i.e., schools, workplaces) [300,301]. Other environmental/occupational exposures associated with increased risk of lung cancer are chromium, nickel, and arsenic [302]. Pulmonary fibrosis appears to increase the risk of developing lung cancer even after controlling for the effect of smoking [303]. HIV and HPV infection may also increase the risk of developing lung cancer, although it is unclear if this observation is being driven predominantly by smoking exposures [304–307].

Genetic factors are also important. The most common genetic risk factors are mutations in EGFR (epidermal growth factor receptors) and ALK (anaplastic lymphoma kinase) [308,309]. EGFR mutations are more common in Asian populations [310].

As NSCLC is the most common lung cancer, we will focus this part of our review on this type of lung cancer. We will first explain the genetic mutations of autophagy in this type of the lung cancer. Then we will discuss how changes in metabolism could affect autophagy in NSCLC.

4.2. Modulation of Autophagy through Genetic Changes in NSCLC

Components of the Rho GTPase signaling pathway are found to be significantly mutated in NSCLC. For example, inactivating mutations in the Rho GTPase activating protein (RhoGap) ARHGAP35 (p190RhoGAP) are found in ~6% of lung squamous cell carcinoma (LUSCs), which will result in increased RhoA GTPase activity [3]. Autophagy and Rho GTPase signaling show a reciprocal regulation [311]. Previously, it was shown that knockdown of ROCK1 (Rho-associated kinase 1), a downstream effector of RhoA, was found to enhance starvation induced autophagy [312]. Also, increased ROCK signaling inhibited autophagy whereas, inhibition of ROCK resulted in augmented autophagy flux with increased size of early and late autophagic structures [313]. The authors suggested that ROCK1 signaling delimits the elongation phase and eventual size of newly formed autophagosomes [313]. Subsequently, it was found that ROCK1 promoted starvation induced autophagy through phosphorylation of BECN1 (ATG6) to prevent BECN1-BCL2L1 interaction [314]. Sequestosome-1 (p62 SQSTM1), an autophagy receptor, sequesters RhoA for autophagic degradation [315]. Also, knockdown of ATG5 results in enhanced RhoA levels and defective cytokinesis, increasing aneuploidy and motility [315,316]. Knockout (KO) of Atg5, Atg7, and Ulk1 in Mouse Embryonic Fibroblasts (MEFs) resulted in increased cell motility with an amoeboid morphology [317]. Tumor cells have two major forms of motility, mesenchymal and amoeboid-type movements, controlled by the Rac1 and RhoA GTPases, respectively [318]. Interaction with p62 SQSTM1 results in degradation of the Rho guanine nucleotide exchange factor ARHGEF2 (GEF-H1) [317]. Atg7 KO cells show increased ARHGEF2 and RhoA activity [317]. Lung ADDs show mutation in ARHGEF2 gene (4%); however, the biological consequence of these mutations is not known at this time [3]. Overall, enhanced RhoA activity increases stress induced autophagy and motility, which in turn sets up a negative feedback loop through autophagy mediated degradation of RhoA and its GTP exchange factor ARHGEF2. It has been recently reported that circular RNA Rho GTPase activating protein 10 (circARHGAP10) is an important factor for the development of NSCLC [319]. circARHGAP10 has been shown to be upregulated in NSCLC tissues, cells, and serum-derived exosomes. On the other hand, serum-derived exosomes increased circARHGAP10 expression in NSCLC cells [319]. miR-638 is a target of circARHGAP10 and is involved in its effect on proliferation, migration, invasion, and glycolysis in NSCLC cells [319]. Another investigation showed that low expression of ARHGAP6 is linked to increased metabolic activity in NSCLC, which confirms ARHGAP6 is a potential tumor suppressor in NSCLC [320]. Therefore, it could be concluded that there might be an indirect link between the effect of small Rho GTPase on glycolysis via regulation of autophagy.

The BCL2L1 gene is focally amplified in ~8% of lung LUSCs and 3% of lung adenocarcinoma (LUADs) [3]. BCL2L1 binds Beclin-1 [321] inhibiting its ability to activate autophagy [322,323]. Therefore, elevated levels of BCL2L1 would be expected to inhibit autophagy induction [323]. Also, elevated levels of BCL2L1 would also be anti-apoptotic through binding of pro-apoptotic proteins such as BAX and BAK [324]. This inhibition of apoptosis would also impart drug resistance to tumor cells [325]. It is still an open question whether BCL2 and BCL2L1 can alter autophagy directly [326]. One study using BAX, BAK1 knockout cells, to prevent apoptosis induction, showed that overexpression of BCL2, MCL1, and BCL2L1 in the knockout cells did not alter autophagy [327,328]. Only when BAK and BAX were present, apoptosis induced autophagy was activated. This suggested that BCL2 like proteins regulate autophagy indirectly by inhibiting BAX/BAK1 mediated apoptosis [327,328]. A follow up study, from another group, showed that the BH3 peptidomimetic drug ABT-737 induced autophagy in BAX/BAK1 double knockout cells when longer durations and higher doses were used, which correlated with disruption of BCL2-BECN1 binding [329]. However, a further study from Reljic et al. suggested that higher doses of BH3 peptidomimetics caused off target effects [330]. Using the cBioPortal.org web site and TCGA data, LUAD patients with BCL2L1 amplification

showed a significant reduction in progression-free survival, but not overall survival (**Figure 8A,B**). However, the number of patients with amplified BCL2L1 was small (n=7) and more patients with this genotype should be studied [1–3]. Further studies are needed to determine whether the effects of BCL2L1 amplification is due to alterations of apoptosis or autophagy. One of the hallmarks of cancer is evasion of apoptosis [331,332], which is associated with an increase in invasion and chemo-resistance [333]. A part of the decrease of apoptosis in tumor cells is correlated with changes in the balance between the Bcl2 family pro- and anti-apoptotic proteins [334]. Therefore, the process of apoptosis, autophagy, and the metabolic status of cancer cells including NSCLC tumor cells are tightly linked to Bcl2 family proteins and the genetic changes of this family could have a direct effect on regulation of the tumor cell response to chemotherapy or tumor invasion.

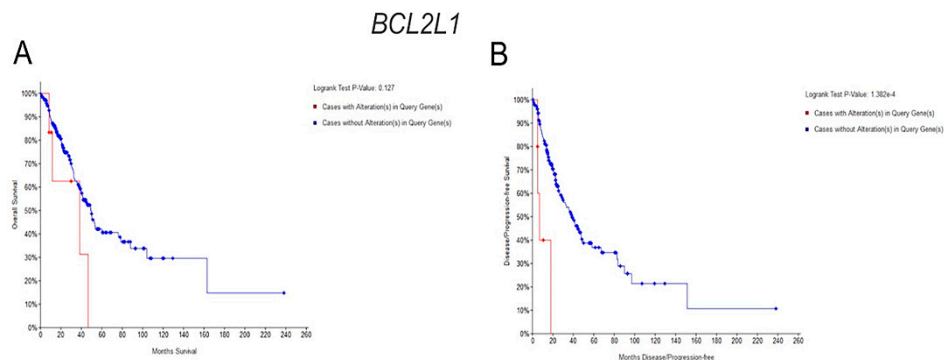


Figure 8. A: Overall Survival Kaplan-Meier Estimate of LUAD cancer patients with BCL2L1 gene amplification (red) or without (blue). B: Disease/Progression-free Kaplan-Meier Estimate in LUAD cancer patients with BCL2L1 gene amplification (red) and without (blue). Graph from Oncomine.org site using TCGA cancer data [1–3].

The frequent mutation in PI3 kinase signaling pathway genes in lung tumors results in activation of the mTORC I kinase complex, which in turn would inhibit autophagy (for review [335]). This suppression of autophagy by oncogenes or tumor suppressors may cause an acceleration of early-stage tumor formation. In a K-rasG12D induced mouse model of NSCLC, it was shown that knockout of Atg5 resulted in increased tumor growth during early stages compared with autophagy competent mice [336]. The accelerated early oncogenesis was due to increased infiltration of FOXP3+ regulatory T cells, which subverted immunosurveillance [336]. However, the Atg5 knockout mice showed increased overall survival due to reduced progression of adenomas to adenocarcinomas, which could be overcome by Tp53 loss [336]. Another study using Atg7 knockout mice showed that autophagy was needed for sustained K-ras induced tumor cell proliferation and progression [204]. The lack of Atg7 resulted in oncocyoma formation due to accumulation of morphologically abnormal mitochondria [204]. Tp53 loss allowed progression to adenocarcinomas in this study, however, the acceleration of early oncogenesis was not seen [204]. It was previously shown that wild type TP53 under drug or stress treatments inhibits mTOR1 kinase complex activity and in turn activates autophagy [337]. In tumors with TP53 loss, mTOR1 would not be inhibited resulting in reduced stress induced autophagy. Therefore, inhibition of autophagy may be another tumor suppressor function of TP53 [337].

4.3. Autophagy, Glucose Metabolism, and lung cancer

As we have discussed in previous sections, glucose metabolism is tightly linked to autophagy in different types of cancers. In this section, we focus the discussion on the impact of glucose metabolism and autophagy in lung cancer.

LKB1 is a master tumor suppressor that limits cell growth through repression of mammalian target of rapamycin complex 1 (mTORC1) and activation of AMPK to control metabolism. Therefore, the loss of LKB1 leads to uncontrolled mTORC1 activation, activation of HIF-1 α , and consequently

angiogenesis and the Warburg Effect [338–340]. Co-mutations in the KRAS proto-oncogene and the LKB1 tumor suppressor gene frequently occur in hyper-metabolic and aggressive human lung adenocarcinoma tumors. mTORC1 is hyperactive in LKB1/KRAS mutant lung adenocarcinoma cancer cells, and thus targeting this pathway by mTOR inhibitors might represent an effective way of treating lung adenocarcinoma [341,342]. In 2018, researchers were able to use the coupling of [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET)/computed tomography (CT) imaging to quantitative immunohistochemistry (qIHC) as an effective method to measure metabolic changes and therapeutic responses caused by a selective catalytic mTOR kinase inhibitor in mouse models of lung cancer. Their analysis showed that the mTOR inhibitor MLN0128 could suppress tumor growth and glycolysis in genetically engineered mouse models (GEMMs) of lung cancer with KRAS and LKB1 co-mutations as shown by reduced 18F-FDG consumption [343]. Interestingly, in addition to the AMPK-mTOR signaling pathway, SIRT3/ HIF-1 α was significantly upregulated in KRAS mutant human lung adenocarcinoma lines (H460, A549, and H358) [344]. Lian-Xiang Luo demonstrated that the simultaneous use of an antitumor (Honokiol) and an autophagy inhibitor, 3-methyladenine (3-MA) triggered pro-death autophagy through activating mitochondrial SIRT3, suppressing HIF-1 α expression, and disrupting oncogenic KRAS-mediated RAF/MEK/ERK and PI3K/AKT/mTOR signaling pathways [344]. The last step of glycolysis is the conversion of PEP to pyruvate and ATP, which is catalyzed by PK. In KRAS mutant cells, PKM2 is hyperactivated and acts as a histone kinase in the nucleus and upregulates the expression of c-Myc. Their overexpression affects metabolic functions including the enhanced expression of glucose transporter GLUT1, the activity of glycolytic enzymes (HK2, PFK, enolase1), and LDHA with the overproduction of lactic acid and non-metabolic ones (up-regulation of autophagy). Although PKM2 activates the mTOR pathway resulting in a block in autophagy in KRAS mutants. Autophagy is hyperactive in KRAS mutant cancer cells [345]. M Morita used in PKM2 mutant lung cancer mouse models (KRASG12D or KRASG12V) and in SCLC cells [346]. Besides KRAS, oncogenic promoters such as the EGFR support glycolytic metabolism in lung tumors. EGFR signaling activates the class I PI3K-AKT-mTORC1 pathway. AKT and mTORC1 phosphorylate Beclin1 on serine residues, leading to downregulation of VPS34 activity and autophagy. In contrast, ULK1 and AMPK stimulate autophagy by phosphorylating Beclin1 and promoting the formation of the active Beclin1-VPS34 complex. mTORC1 also suppresses autophagy initiation by phosphorylating and inhibiting ULK1. These EGFR-dependent events are blocked by tyrosine kinase inhibitors (TKIs) [347]. Therefore, it can be concluded that autophagy plays an important role in KRAS and EGFR mutant lung tumors through small Rho GTPase and PI3-AKT-mTORC1 pathway.

M Ye et al. showed that overexpression of GLUT1 and MCT-4 led to a significant increase in glycolysis and autophagy in ER6 cells (erlotinib-resistant sub-line of HCC827) compared to EGFR-TKI sensitive HCC827 lung adenocarcinoma cell lines. They demonstrated that the combination of an AKT inhibitor (MK2206), to suppress AKT phosphorylation or autophagy, with glucose deprivation and a GLUT1 specific inhibitor (STF-31) could tackle the resistance to erlotinib in NSCLC [348]. Other compounds that target the EGFR are Flavonoids (natural products with variable phenolic structures that reduce the risk of cancer). A recent study revealed that Scandanolone (a natural isoflavonoid) directly attaches to the ATP-binding site of EGFR to impede the phosphorylation of AKT/ERK signaling pathway, which is essential for sensitizing SK-MEL-28 melanoma cell lines to intrinsic apoptosis and blocking autophagy flux. In fact, exposure to Scandanolone inhibits the AKT/ERK pathway, leading to an increase in Bad, one of the BH3-only proteins, and a reduction in Bcl-2, an anti-apoptotic protein, disrupting not only the inhibitory interactions between Beclin-1 and Bcl-2, but also the activation of the lysosomal protease Cathepsin B which induces the induction of autophagy in these cells [348]. Another study examined whether adding an additional isopentenyl group to the Scandanolone structure would improve its anticancer effect. This new antitumor compound named Final-2 could not only suppress cancer cell growth by promoting apoptosis and blocking autophagy, but also by inhibiting the expression of the oncogenes KRAS, c-Myc, and glucose transporters (GLUTs) such as GLUT1, GLUT3, and GLUT4 which resulted in downregulation of glucose metabolism in human lung cancer cells A549 [349].

It has been shown that under stress conditions (hypoxia, glucose deprivation, low pH, ROS accumulation, and Ca²⁺ homeostasis perturbation), lung cancer cells experience ER stress and activate GRP78/BiP-related unfolded protein response (UPR) signaling. Upon ER stress, GRP78/BiP can trigger autophagy to improve the survival of cancer cells through three different UPR pathways including eukaryotic translation initiation factor 2 alpha kinase 3/PKR-like ER kinase (EIF2AK3/PERK), endoplasmic reticulum to nucleus signaling 1/inositol-requiring enzyme 1 (ERN1/IRE1) and activating transcription factor 6 (ATF6), which target the ATG16L1 complex, MAPK/JNK and X-box binding protein 1 (XBP1), and AKT-mTOR pathway, respectively [350–353]. It has been reported that overexpression of GRP78 is often seen in advanced-stage lung cancer, which is associated with a poor prognosis [354]. A recent study has reported that inhibition of ATPase activity of GRP78 by a thiazole benzenesulfonamid (HA15) provokes ER stress-mediated UPR and induces pro-apoptotic autophagy in lung cancer cell line A549 [355]. Glucose starvation induces ER stress-related GRP78 in NSCLC cells, leading to autophagy as a cyto-protective process. In this regard, the microtubule cytoskeleton is involved in autophagy signaling and β III-Tubulin is one of the β -tubulin isotypes overexpressed in glucose-starved NSCLC cells. On the other hand, GRP78 interacts with β III-tubulin, however, the functional consequences of this association are unknown. Tubulins, and in particular β III-tubulin, associate with a variety of glycolytic enzymes including PK, phosphofructokinase, aldolase, hexokinase, GAPDH, and LDH. These observations suggest an inherent link between the microtubule cytoskeleton, glycolysis, autophagy, and the initiation of ER stress responses [356]. β III-Tubulin enables rapid GRP78/Akt activation in response to glucose starvation and decreases the reliance of cells on glycolytic metabolism to maintain cell survival and proliferation. Amelia L. Parker in 2016 indicated that suppression of high β III-tubulin expression with 4-phenylbutyric acid and N-acetylglucosamine ameliorates the ER stress and reduces autophagy through delaying the association of GRP78 with Akt in glucose-starved NSCLC cells [357]. The major stressors influencing autophagy flux are Ca²⁺ homeostasis disturbances and glucose starvation. Thus, voltage and ligand-gated calcium channels (such as T-type, L-type, and IP₃-R), and GLUTs, which are often upregulated in cancer, are also targets for autophagy regulation. Both Ca²⁺ and glucose influx perturbations might be signals for UPR and ER stress activation, leading to the ER chaperones such as GRP78/BiP stimulating autophagy through three different molecular pathways such as ERN1/IRE1-JNK-Bcl-2, EIF2AK3/PERK-eIF2a-ATF4, or ATF6-XBP1-ATG. In addition, both starvation and Ca²⁺ perturbations may lead to activation of ER stress-mediated autophagy in cancer cells via distinct Ca²⁺ channel activation, CaMKK β , which mediates AMPK-dependent inhibition of mTORC1 or by activating the IP₃-R-Beclin1-Bcl-2 pathway. Therefore, the development of Ca²⁺ channel and GLUTs blockers would be a novel cancer therapy. Hong-Kun Rim et al. revealed that co-blocking T-type Ca²⁺ channel and GLUT with KYS05047 and KYS05090 synthesized compounds can induce autophagy and apoptosis in human lung adenocarcinoma A549 cells and xenografts resulting in elevated ROS generation and reduced intracellular Ca²⁺ levels and glucose uptake [353,358–360].

Glutamine, the blood's most abundant amino acid, is metabolized through glutaminolysis, catalyzed by glutaminase (GLS) and leucine-dependent glutamate dehydrogenase (GDH), to produce α KG for the Krebs cycle, nucleotides, and other amino acids. The expression level of GLS is regulated by the oncogene c-Myc, and its upregulation is a hallmark of tumor growth. In fact, enhancing glutaminolytic α KG production stimulates lysosomal translocation and activation of mTORC1. mTORC1 (master switch for cell proliferation and autophagy) is regulated by glutaminolysis [361]. Recently, RC Bruntz et al. by using [13C6]-glucose and [13C5,15N2]-glutamine as tracers showed that Selenite inhibited glutaminolysis by suppressing GLS1 expression and inducing excess ROS production, which mediates autophagy and eventual cell death in NSCLC A549 cells [362]. The upregulated glutaminolysis is a feature of cancer cell metabolism, activated by extracellular lactate signaling. Under oxygenated conditions in the tumor environment, lactate enters the cells via MCT1, stabilizing hypoxia-inducible factor-2 α (HIF-2 α), and then transactivating c-Myc. This in turn activates the expression of glutamine transporters (LAT1 and ASCT2) and glutaminase 1 (GLS1), resulting in an increased proportion of glutamine absorption by tumor cells and triggering OXPHOS [363,364]. Forming an acidic tumor microenvironment is a common event in lung cancer

due to the production of lactate by the Warburg Effect. For lung cancer cells to survive in such a situation in-vivo or in-vitro, autophagy is induced by the acidic pH through ER stress-related GRP78. Glucose starvation and inhibition of MCT-1 with α -cyano-4-hydroxycinnamate (CHC) in mice injected with hypoxic Lewis lung carcinoma (LLC) cells resulted in decreased tumor growth [365]. Knockdown of GRP78 by siRNA reduced autophagy activation under acidic conditions in the human lung cancer cell lines (A549 and NCI-H226) and enhanced acid-induced apoptosis [366]. Glucose depletion (GD) induces necrotic cell death in A549 lung carcinoma cells, activating an inflammatory response due to the release of high-mobility group box 1 (HMGB1). SC Lim et al. revealed that sodium salicylate, an active metabolite of aspirin, could inhibit HMGB1 release, Cu/Zn superoxide dismutase1 (SOD1) release, and ROS production in A549 cells cultured in GD medium, which in turn led to the anti-inflammatory effect. Moreover, aspirin could activate AMPK, inhibit mTOR to induce autophagic cell death, and suppress tumor development [367–369]. Glutamate oxaloacetate transaminase 1 (GOT1) by catalyzing the conversion of aspartate to oxaloacetate (OAA) provides metabolites necessary for gluconeogenesis, and thus GOT1 is involved in the maintenance of redox homeostasis and the regulation of glycolytic metabolism in normal cells [370], while inhibition of GOT1 leads to increased glucose utilization and lactate production, resulting in a decrease in cellular pH [371]. X Zhou in 2018 demonstrated that in GOT1-null 143B osteosarcoma cells or GOT1 siRNA knockdown in A549 lung cancer cells resulted in the elevated expression of autophagy-related genes (ATG5 and Beclin1) and increased secretion rate of lactate compared with wild type cells [371]. Placing these cells in a glucose-free culture medium caused a reduction in cell viability [371].

Nickel compounds are mainly associated with metabolic changes in sino-nasal and lung cancers. YT Kang et al. 2017 documented that hexokinase 2 (HK2), involved in the first step of glycolysis, plays a significant role in Nickel-induced autophagy in lung bronchial epithelial cells (BEAS-2B). They determined that the inhibition of HK2 by the antihyperglycemic drug metformin and the knockdown of lipocalin 2 (LCN2) by shRNA mitigated NiCl₂-mediated autophagy and induce apoptosis in BEAS-2B cells [372]. VK Chaudhri et al. by evaluating two cell groups including primary human lung tumor CAFs and “normal” fibroblasts (NF) isolated from nonneoplastic lung tissue located at least 5 cm away from the tumor, determined that metabolic alterations are not limited to cancer cells. They demonstrated that the reduction of amount of glucose in the medium from 25 to 5 mmol/L also increased dipeptides and autophagy in NFs [373].

We have summarized the role of various glycolytic enzymes in relation to autophagy in lung cancer in **Table 4**.

Table 4. The effect of enzymes involved in glycolysis on autophagy in lung cancer.

Enzyme Name	Enzyme Isoform	Type of Cancer	Molecules	Roles in Glycolysis and Autophagy	Ref.
HK	HK2	NSCLC	2-DG	Induce autophagy and apoptosis by increasing LC3II and cleaved caspase3 protein level.	[374]
		NSCLC	SiRNA	Inhibit cancer cell proliferation and tumorigenesis through decreasing glycolysis and HK2 expression at both the mRNA and protein levels.	[375]
		NSCLC	miR-143	Inhibit glycolysis and autophagy by knockdown of HK2 and Atg2B.	[376]
PFKFBs	PFKFB3	NSCLC	Erlotinib drives	Reduce EGF-mediated increase in glycolysis.	[377]
	PFKFB4	SCLC	Ibrutinib	Inhibit autophagy by targeting Erk.	[378]

GAPDH	-	NSCLC	SiRNA	Reduce glycolysis and cease tumor cell proliferation.	[127]
PK	PKM2	NSCLC	pshRNA	Induce autophagy and apoptosis.	[379]
LDH	LDHA	Lung and Breast Cancer	WZB117 & ShRNA	Reduce glycolysis and induction of apoptosis.	[380]
HIF	HIF-1	NSCLC	SP600125	Inhibit hypoxia-induced autophagy by targeting Beclin-1 protein.	[380]
		NSCLC	Chloramphenicol	Inhibit hypoxia-induced autophagy.	[381]
Lactate	-	NSCLC	SiRNA	Reduce pH-stimulated autophagy by knockdown of Beclin-1 protein and ER stress marker protein (GRP78).	[366]

4.4. Lipid Metabolism Regulation of Autophagy in Lung Cancer

4.4.1. HMGCR Inhibition

Statins (inhibitors of HMGCR) are widely used for lowering serum cholesterol. They also have several pleiotropic effects including their potential effects in different types of cancers [200,382]. A recent xenograph study in a nude mice by Yang et al. reported that use of the statin fluvastatin could significantly inhibit the metastasis of lung adenocarcinoma cells to bone. The anti-metastatic effect of fluvastatin was shown to be due to the induction of autophagy in lung adenocarcinoma cells. The chemical inhibition of autophagy by 3-methyadenine (3-MA) or Bafilomycin A1 (Baf A1) and genetic inhibition of autophagy by knocking down Atg5 or Atg7 hampered the suppressive effects of fluvastatin on bone metastasis of lung cancer cells. These findings highlight the importance of mevalonate pathway inhibition by statins (through HMGCR inhibition) on the regulation of autophagy and how this leads to the suppression of bone metastasis of lung cancer cells [383].

Another statin that has been extensively studied in cancer is lovastatin. It has been reported that lovastatin has inhibitory effects on growth and proliferation of NSCLC adenocarcinoma lung cancer cells A549 ([384]. In addition, it increases the sensitivity of A549 lung cancer cells to ionizing radiation and inhibits their colony forming ability. Interestingly, these effects by lovastatin were reversible when mevalonate was used in the treatment as well [384]. This indicates the effects of lovastatin were dependent on its ability to inhibit the mevalonate pathway. In this same study, treatment of A549 cells with lovastatin resulted in the induction of cell death and induced AMPK phosphorylation, an upstream regulator of autophagy by directly activating ULK1 through phosphorylation [384]. Collectively, these results show that the lovastatin-induced cell death could be due to AMPK-mediated lethal autophagy. These results emphasize the crucial role that the mevalonate pathway can play on the regulation of autophagy which consequently impacts lung cancer cells' proliferation and clonogenicity and improves their sensitivity to ionizing radiation [383].

4.4.2. SPHK1

The expression of SPHK1 is significantly increased in NSCLC patients. In a study by Zhu et al [385] it was found that SPHK1 expression is highly elevated in A549 cells. They showed that SPHK1 overexpression is enhanced in A549 cells while SPHK1 knockdown prevented the migration and invasion of these cells. In fact, the expression of E-cadherin was reduced, and expression of SNAIL was increased in overexpressed cells. More importantly, SPHK1 induced AKT activation. Since the mTOR-AKT pathway is a master regulator of autophagy, it is safe to say that SPHK1 promotes the invasion and migration of lung cancer cells simultaneously with (and possibly through) autophagy inhibition [385]. This evidence highlights that targeting SPHK1 is a promising candidate for NSCLC

treatment. Consistent with these findings, another research group evaluated the expression of SPHK1 in tissues obtained from 176 NSCLC patients using immunohistochemistry (IHC) [386]. The expression of SPHK1 was correlated with clinicopathological factors and it was shown that patients with a high expression of SPHK1 that were treated with adjuvant platinum-based chemotherapy had a significantly lower survival rate. This indicates that even doing IHC on tissues from NSCLC patients can be a potential predictive tool for the survival of NSCLC patients.

In addition, another study used SPHK1 expression levels to predict survival and progression in NSCLC patients. Findings from this study revealed that SPHK1 expression was significantly increased in 218 tissues samples from NSCLC patients [387]. This was associated with inhibition of doxorubicin- or docetaxel-induced apoptosis and induction of anti-apoptotic factors. Conversely, chemical inhibition and knockdown of SPHK1 remarkably increased NSCLC cells' sensitivity to apoptosis triggered by anticancer agents both in vitro and in vivo. Regarding the association of SPHK1 and autophagy, it was also shown that high SPHK1 expression induced the activation of the PI3K/AKT pathway, which as mentioned earlier can inhibit autophagy via mTOR signaling. Interestingly, inhibition of the PI3K-AKT pathway failed to induce anti-apoptotic effects by SPHK1, therefore highlighting this pathway and its downstream pathway (autophagy) as a mediator of SPHK1 effects on NSCLC cells. In agreement with these findings, it was found that SK1-I, a competitive SPHK1 inhibitor, induces apoptosis in cancer cells and suppresses the metastasis of cancer cells into lymph nodes [388]. As mentioned in previous sections, phosphoinositides can modulate autophagy. Also, any deregulation in the function of PI3K leads to autophagy deregulation because PI3K is part of the PI3K-AKT-mTOR pathway [389].

4.4.3. PA

Phospholipase D (PLD) is the enzyme that hydrolyses phosphatidylcholine (PC) to PA and choline [390]. The expression and activity of a single nucleotide polymorphism (SNP) in the Phospholipase D1 (PLD1) gene (SNP A2698C) is significantly increased in a variety of human cancers [391]. It has been shown that PLD1 expression is significantly increased in lung surgical specimens obtained from NSCLC patients compared to normal lung tissues [392]. Moreover, PLD1 has been associated with the development and aggression of lung cancer [387].

As discussed in earlier sections, PA is involved in 1) formation of autophagosome curvature and 2) inhibition of mTOR and therefore induction of autophagy [78,393]. It can be suggested that higher expression of PLD1 in NSCLC leads to higher production of PA and consequently higher rates of autophagy induction in NSCLC cells [391]. Also, it was reported some time ago that upon activation (through bradykinin and sphingosine 1), PLD1 is involved in the PKC pathway in NSCLC A549 cells [394,395] which can regulate autophagy. This further suggests regulation of autophagy by lipid metabolism in NSCLC.

Lipin-1 is the enzyme that converts PA to diacylglycerol (DAG) [396]. Lipin-1 expression is significantly increased in NSCLC cell lines and patient tissues. It has recently been shown that the elevated expression of Lipin-1 is associated with poor prognosis of NSCLC patients. Moreover, Lipin-1 suppression greatly reduces the growth and viability of NSCLC cells while it has almost no significant effects on non-cancerous cells in the lung [397]. In addition, the same research group demonstrated that loss of Lipin-1 sensitized NSCLC cells to cisplatin. Since PA is involved in the formation of autophagosome curvature [390], disruption of Lipin-1 can potentially help accumulate the PA levels and consequently boost autophagosome formation during autophagy activation. This can potentially reveal the impact of PA in autophagy regulation during NSCLC progression. These findings suggest that targeting Lipin-1 (and therefore the conversion rate of PA to DAG) in combination with other NSCLC anticancer agents could be a promising treatment intervention for lung cancer [397].

Interestingly, it has been observed that the levels of Interleukin-8 (IL-8 or CXCL8), which is a pro-inflammatory chemokine, are significantly elevated in different cancers including NSCLC. This increased IL-8 level has been associated with enhanced activity of PLD and the activation of AKT/mTOR, which can directly regulate autophagy [391]. Furthermore, IL-8 activates PLD, which

consequently converts PC to PA. These findings similarly show the involvement of PDL (and hence PA) in the regulation of autophagy in lung cancer cells.

Due to their importance in cancer development and progression, targeting PDL1 and its signaling molecules has been suggested as a treatment strategy in different cancers with an increased PLD1 activity and expression [390].

4.4.4. Peroxisome Proliferator-Activating Receptors (PPARs)

As mentioned previously, PPARs are ligand-dependent nuclear transcription factors. In order to be functional as transcription factors, PPARs need to bind to lipid ligands (e.g., oleic acid, linoleic acids, linolenic acids, prostaglandins, eicosanoids, and oxidized lipids) through lipid-binding proteins [246–248]. A study [398] showed that treatment of A549 NSCLC cells with troglitazone (an activator of PPAR γ) induced the conversion of LC3-I to LC3-II and increased the degradation of p62, indicating activation of autophagy flux while inducing apoptosis in A549 cells. Consistently, the activation of PPAR γ and subsequently autophagy activation was inhibited when cells were treated with a PPAR γ antagonist, GW9662. This highlights troglitazone as a potential candidate for combination therapy of apoptosis resistant NSCLC. Moreover, another study on human NSCLC cell lines HCC827 and H1650 demonstrated that PPAR γ agonists sensitize PTEN-deficient lung cancer cells to EGFR TKIs via autophagy induction [399]. One of the mechanisms of developing resistance in lung cancer is through PTEN loss, which contributes to resistance to EGFR TKIs [400]. It was shown that PPAR γ agonists increased the expression of PTEN and consequently inhibited the PI3K-AKT signaling pathway, which will activate autophagy through mTOR inhibition. This results in significant sensitivity to gefitinib (an EGFR TKI). The mechanism of this sensitivity to EGFR-TKIs was found to be the induction of autophagy. In fact, the findings by this group showed that PPAR γ agonists induced higher levels of LC3-II accumulation and degradation of p62 in NSCLC cells. Also, genetic silencing of ATG5 eliminated this potentiation effect by PPAR γ agonists. Therefore, combination use of PPAR γ agonists and EGFR TKIs have recently been suggested for treatment of lung cancer patients. In an animal study [401], it was shown that the treatment of mice with pioglitazone (synthetic PPAR γ ligand) remarkably prevented lung tumor formation induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1butanone (NNK). Also, it was found that endogenous PPAR γ was decreased well before lung tumor formation, indicating a role for the endogenous PPAR γ molecular pathway in lung cancer development. These findings show that the potential increase in the activity of PPAR γ using its ligands not only could be inhibitory for lung tumor formation but also beneficial for the treatment of lung cancer. Moreover, assessment of the activity levels of PPAR γ may be useful as biomarkers for lung cancer.

4.4.5. Omega-3 PolyUnsaturated Fatty Acids (n-3 PUFAs) (Docosahexaenoic Acid (DHA), Docosahexaenoyl Ethanolamine (DHEA), EPA)

Free lipids can also regulate autophagy during lung cancer, although only a handful of studies have investigated this relationship. n-3 PUFAs and in particular, DHA or EPA, have been defined as important preventive lipids against lung cancer development [402,403]. They can exert their effects through different ways including cell surface receptor functions, membrane fluidity, and enhancement of oxidative stress, all of which might induce autophagy [403]. One study [404] demonstrated that both DHA and EPA caused the formation of autophagosomes in a concentration-dependent fashion in NSCLC A549 cell line. This was confirmed by the finding that treatment of A549 cells with autophagy inhibitor, 3-MA, reversed the formation of autophagosomes. This autophagy inhibition also prevented apoptosis (reduced activation of caspase-3/7) and increased cell viability, showing that DHA and EPA-induced autophagy acts to enhance apoptotic cell death of A549 cells. It has also been reported that treatment of A549 cells with DHA or EPA induced autophagy in a dose- and time-dependent manner [405]. The results from this study also showed that the anti-tumor effects of DHA and EPA were associated with activation of autophagy.

5. Conclusions and Future Directions

Autophagy plays important roles at different stages of tumor development, progression, and metastasis. During the early stages of tumor development, it prevents tumorigenesis by removal of damaged mitochondria and misfolded proteins, while it supports tumor progression in later stages of tumor formation. Autophagy also regulates tumor metastasis both positively or negatively, but it is dependent on the type of tumor. As we have discussed in our article, both glucose and lipid metabolism can regulate autophagy via different mechanisms to compensate for the high ATP demand of cancer cells as summarized in **Figure 9**. The enzymes of glycolysis can directly interact with the autophagy machinery (HK2) [103] to change their activity or expression levels or directly induce changes in autophagy in tumor cells (PFKFB4) as an adaption to cellular stress conditions [120,121]. On the other hand, the major adaptations of lipid metabolism observed in cancer is generally associated with changing the autophagy pathway in favor of increased aggressiveness of cancer cells.

Therefore, targeting lipid metabolism or glycolysis is an attractive therapeutic strategy. However, a greater understanding of the specific roles played by lipid and glycolytic metabolites and/or enzymes involved in lipid metabolism and glycolysis in cancer is still needed. Our current knowledge of the role that these pathways can play in the regulation of autophagy in different cancers is very much limited to a few studies. Future studies will undoubtedly provide us with promising effective candidates for the prevention and treatment of different cancers.

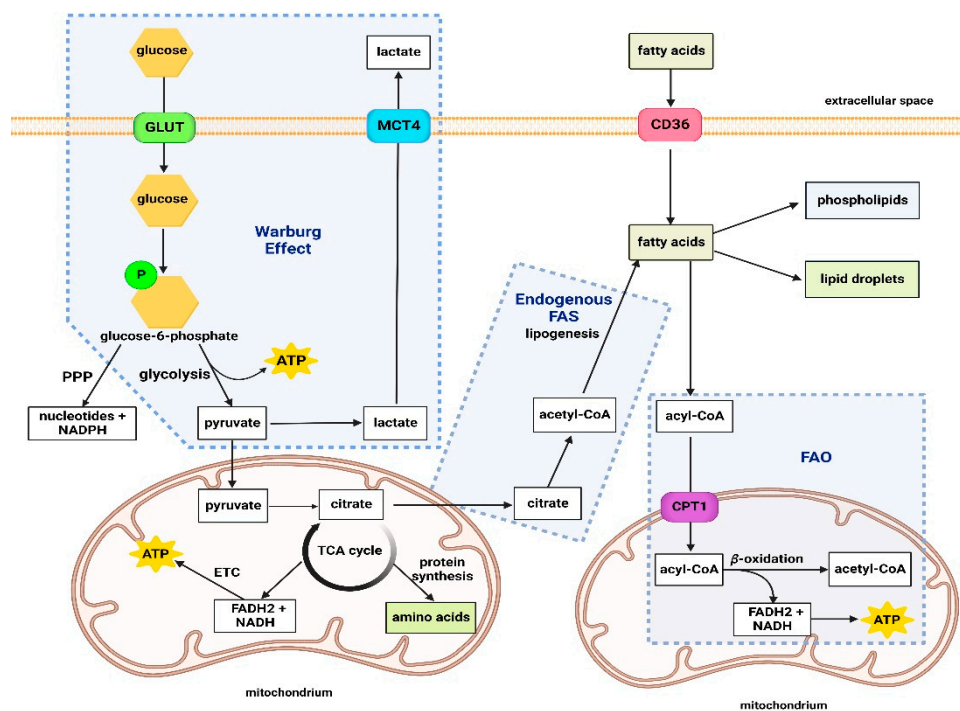


Figure 9. Schematic representation highlighting the metabolic pathways upregulated in cancer. In tumour cells, the uptake of glucose and aerobic glycolysis (the Warburg Effect) are upregulated for rapid ATP production. The abundance of lactate that is produced is excreted into the extracellular space/tumour microenvironment. Some pyruvate is shunted into the mitochondrion for OXPHOS. The excess glucose feeds into biosynthesis, such as nucleotide, protein, and lipid synthesis, which supports uncontrolled proliferation. Altered glucose metabolism is linked to altered lipid metabolism in tumour cells, as glucose is the major substrate for lipid synthesis. Both endogenous fatty acid synthesis and fatty acid uptake are upregulated in tumour cells. The fatty acids can be subsequently used for ATP production through β -oxidation, which is also upregulated in tumour cells and supports uncontrolled growth and proliferation. ATP, adenosine triphosphate; CPT1, carnitine palmitoyl

transferase 1; ETC, electron transport chain; FAO, fatty acid oxidation; FAS, fatty acid synthesis; GLUT, glucose transporter; MCT4, monocarboxylate transporter 4; PPP, pentose phosphate pathway; TCA cycle, tricarboxylic acid cycle.

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References

1. Cerami, E.; Gao, J., et al., The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer discovery* 2012, 2 (5), 401-4.
2. Gao, J.; Aksoy, B. A., et al., Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Science signaling* 2013, 6 (269), pl1.
3. Campbell, J. D.; Alexandrov, A., et al., Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nat Genet* 2016, 48 (6), 607-16.
4. Kotowski, K.; Rosik, J., et al., Role of PFKFB3 and PFKFB4 in Cancer: Genetic Basis, Impact on Disease Development/Progression, and Potential as Therapeutic Targets. *Cancers (Basel)* 2021, 13 (4).
5. Chaudhry, R.; Varacallo, M., *Biochemistry, Glycolysis*. [Updated 2019 Apr 21]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2020.
6. Esmaeili, Y.; Yarjanli, Z., et al., Targeting autophagy, oxidative stress, and ER stress for neurodegenerative disease treatment. *J Control Release* 2022, 345, 147-175.
7. Shojaei, S.; Suresh, M., et al., Autophagy and SARS-CoV-2 infection: A possible smart targeting of the autophagy pathway. *Virulence* 2020, 11 (1), 805-810.
8. Dalvand, A.; da Silva Rosa, S. C., et al., Potential role of TGFβ and autophagy in early cerebellum development. *Biochem Biophys Res Commun* 2022, 616, 101358.
9. Mizushima, N.; Komatsu, M., Autophagy: renovation of cells and tissues. *Cell* 2011, 147 (4), 728-41.
10. Ghavami, S.; Gupta, S., et al., Autophagy and heart disease: implications for cardiac ischemia-reperfusion damage. *Curr Mol Med* 2014, 14 (5), 616-29.
11. Ghavami, S.; Zamani, M., et al., Epigenetic regulation of autophagy in gastrointestinal cancers. *Biochim Biophys Acta Mol Basis Dis* 2022, 1868 (11), 166512.
12. Berg, J.; Tymoczko, J., et al., Chapter 17: The citric acid cycle. *Biochemistry*. New York: WH Freeman and Company 2002.
13. Li, W. W.; Li, J., et al., Microautophagy: lesser-known self-eating. *Cellular and molecular life sciences : CMLS* 2012, 69 (7), 1125-36.
14. Cuervo, A. M.; Wong, E., Chaperone-mediated autophagy: roles in disease and aging. *Cell research* 2014, 24 (1), 92-104.
15. Mokarram, P.; Albokashy, M., et al., New frontiers in the treatment of colorectal cancer: Autophagy and the unfolded protein response as promising targets. *Autophagy* 2017, 13 (5), 781-819.
16. Seo, A. Y.; Lau, P. W., et al., AMPK and vacuole-associated Atg14p orchestrate mu-lipophagy for energy production and long-term survival under glucose starvation. *eLife* 2017, 6.
17. Martelli, A.; Omrani, M., et al., New Visions on Natural Products and Cancer Therapy: Autophagy and Related Regulatory Pathways. *Cancers (Basel)* 2022, 14 (23).
18. Goldsmith, J.; Levine, B., et al., Autophagy and cancer metabolism. *Methods in enzymology* 2014, 542, 25-57.
19. Liu, Y.; Shoji-Kawata, S., et al., Posner 960 B, Tran KA, Green DR, Xavier RJ, Shaw SY, Clarke PG, Puyal J, and Levine B. 961 Autosis is a Na⁺, K⁺-ATPase-regulated form of cell death triggered by autophagy-962 inducing peptides, starvation, and hypoxia-ischemia. *Proceedings of the National 963 Academy of Sciences of the United States of America* 2013, 110 (20364-20371), 964.
20. Baghaei, K.; Mazhari, S., et al., Therapeutic potential of targeting regulatory mechanisms of hepatic stellate cell activation in liver fibrosis. *Drug Discov Today* 2022, 27 (4), 1044-1061.

21. Eshraghi, M.; Ahmadi, M., et al., Enhancing autophagy in Alzheimer's disease through drug repositioning. *Pharmacol Ther* 2022, 237, 108171.
22. Habibzadeh, P.; Dastsooz, H., et al., Autophagy: The Potential Link between SARS-CoV-2 and Cancer. *Cancers (Basel)* 2021, 13 (22).
23. Scherz-Shouval, R.; Shvets, E., et al., Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4. *The EMBO journal* 2019, 38 (10), e101812.
24. Barzegar Behrooz, A.; Talaie, Z., et al., Wnt and PI3K/Akt/mTOR Survival Pathways as Therapeutic Targets in Glioblastoma. *Int J Mol Sci* 2022, 23 (3).
25. Sharifzad, F.; Ghavami, S., et al., Glioblastoma cancer stem cell biology: Potential theranostic targets. *Drug Resist Updat* 2019, 42, 35-45.
26. Alizadeh, J.; Lorzadeh, S., et al., Autophagy and cancer metastasis: a Trojan horse. *J Investig Med* 2021, 69 (6), 1145-1147.
27. Brun, P.; Tarricone, E., et al., The regulatory activity of autophagy in conjunctival fibroblasts and its possible role in vernal keratoconjunctivitis. *J Allergy Clin Immunol* 2020, 146 (5), 1210-1213 e9.
28. Samiei, E.; Seyfoori, A., et al., Investigating Programmed Cell Death and Tumor Invasion in a Three-Dimensional (3D) Microfluidic Model of Glioblastoma. *Int J Mol Sci* 2020, 21 (9).
29. Shojaei, S.; Alizadeh, J., et al., Statins: a new approach to combat temozolomide chemoresistance in glioblastoma. *Journal of Investigative Medicine* 2018, 66 (8), 1083.
30. Shojaei, S.; Koleini, N., et al., Simvastatin increases temozolomide-induced cell death by targeting the fusion of autophagosomes and lysosomes. *FEBS J* 2020, 287 (5), 1005-1034.
31. Kawalec, P.; Martens, M. D., et al., Differential impact of doxorubicin dose on cell death and autophagy pathways during acute cardiotoxicity. *Toxicol Appl Pharmacol* 2022, 453, 116210.
32. Dastghaib, S.; Shojaei, S., et al., Simvastatin Induces Unfolded Protein Response and Enhances Temozolomide-Induced Cell Death in Glioblastoma Cells. *Cells* 2020, 9 (11).
33. Stefanek, E.; Samiei, E., et al., A bioengineering method for modeling alveolar Rhabdomyosarcoma and assessing chemotherapy responses. *MethodsX* 2021, 8, 101473.
34. Moghadam, A. R.; da Silva Rosa, S. C., et al., Autophagy modulates temozolomide-induced cell death in alveolar Rhabdomyosarcoma cells. *Cell Death Discov* 2018, 4, 52.
35. Long, J. S.; Kania, E., et al., ATG7 is a haploinsufficient repressor of tumor progression and promoter of metastasis. *Proc Natl Acad Sci U S A* 2022, 119 (28), e2113465119.
36. Bermudez, O.; Marchetti, S., et al., Post-translational regulation of the ERK phosphatase DUSP6/MKP3 by the mTOR pathway. *Oncogene* 2008, 27 (26), 3685-91.
37. Alizadeh, J.; Glogowska, A., et al., Autophagy modulates transforming growth factor beta 1 induced epithelial to mesenchymal transition in non-small cell lung cancer cells. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* 2018, 1865 (5), 749-768.
38. Alizadeh, J.; Shojaei, S., et al., Simultaneous Detection of Autophagy and Epithelial to Mesenchymal Transition in the Non-small Cell Lung Cancer Cells. *Methods Mol Biol* 2019, 1854, 87-103.
39. Gundamaraju, R.; Lu, W., et al., Autophagy and EMT in cancer and metastasis: Who controls whom? *Biochim Biophys Acta Mol Basis Dis* 2022, 1868 (9), 166431.
40. Fell, D.; Cornish-Bowden, A., *Understanding the control of metabolism*. Portland press London: 1997; Vol. 2.
41. Newsholme, E. A.; Start, C., *Regulation in metabolism*. 1973.
42. Morrison, A. J., Cancer cell metabolism connects epigenetic modifications to transcriptional regulation. *FEBS J* 2022, 289 (5), 1302-1314.
43. Wang, X.; An, P., et al., Mitochondrial Metal Ion Transport in Cell Metabolism and Disease. *Int J Mol Sci* 2021, 22 (14).
44. Sekar, M.; Thirumurugan, K., Autophagy: a molecular switch to regulate adipogenesis and lipolysis. *Mol Cell Biochem* 2022, 477 (3), 727-742.
45. Watanabe, S.; Tsujino, S., Applications of Medium-Chain Triglycerides in Foods. *Front Nutr* 2022, 9, 802805.
46. Vance, J. E.; Vance, D. E., *Biochemistry of lipids, lipoproteins and membranes*. Elsevier: 2008.
47. Solinas, G.; Borén, J., et al., De novo lipogenesis in metabolic homeostasis: More friend than foe? *Molecular metabolism* 2015, 4 (5), 367-377.
48. Ameer, F.; Scandiuzzi, L., et al., De novo lipogenesis in health and disease. *Metabolism* 2014, 63 (7), 895-902.
49. Wang, Y.; Yu, W., et al., Acetyl-CoA Carboxylases and Diseases. *Front Oncol* 2022, 12, 836058.
50. Cases, S.; Smith, S. J., et al., Identification of a gene encoding an acyl CoA: diacylglycerol acyltransferase, a key enzyme in triacylglycerol synthesis. *Proceedings of the National Academy of Sciences* 1998, 95 (22), 13018-13023.
51. Yen, C.-L. E.; Stone, S. J., et al., Thematic review series: glycerolipids. DGAT enzymes and triacylglycerol biosynthesis. *Journal of lipid research* 2008, 49 (11), 2283-2301.
52. Fillmore, N.; Alrob, O. A., et al., Fatty Acid beta-Oxidation. *AOCS Lipid library*, doi 2011, 10.

53. Calder, P. C., Omega-3 fatty acids and metabolic partitioning of fatty acids within the liver in the context of nonalcoholic fatty liver disease. *Curr Opin Clin Nutr Metab Care* 2022, 25 (4), 248-255.
54. Gao, Z.; Chen, X., Fatty Acid beta-Oxidation in Kidney Diseases: Perspectives on Pathophysiological Mechanisms and Therapeutic Opportunities. *Front Pharmacol* 2022, 13, 805281.
55. Coleman, R. A.; Lee, D. P., Enzymes of triacylglycerol synthesis and their regulation. *Progress in lipid research* 2004, 43 (2), 134-176.
56. Aguado, B.; Campbell, R. D., Characterization of a human lysophosphatidic acid acyltransferase that is encoded by a gene located in the class III region of the human major histocompatibility complex. *Journal of Biological Chemistry* 1998, 273 (7), 4096-4105.
57. Shi, Y.; Cheng, D., Beyond triglyceride synthesis: the dynamic functional roles of MGAT and DGAT enzymes in energy metabolism. *American Journal of Physiology-Endocrinology and Metabolism* 2009, 297 (1), E10-E18.
58. Le A, e., *The Heterogeneity of Cancer Metabolism*. Springer 2021.
59. Vaupel, P.; Schmidberger, H., et al., The Warburg effect: essential part of metabolic reprogramming and central contributor to cancer progression. *International journal of radiation biology* 2019, 95 (7), 912-919.
60. Liberti, M. V.; Locasale, J. W., The Warburg Effect: How Does it Benefit Cancer Cells? *Trends in biochemical sciences* 2016, 41 (3), 211-218.
61. San-Millán, I.; Brooks, G. A., Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. *Carcinogenesis* 2017, 38 (2), 119-133.
62. Huang, R.; Zong, X., Aberrant cancer metabolism in epithelial-mesenchymal transition and cancer metastasis: Mechanisms in cancer progression. *Critical reviews in oncology/hematology* 2017, 115, 13-22.
63. Sanders, F. W.; Griffin, J. L., De novo lipogenesis in the liver in health and disease: more than just a shunting yard for glucose. *Biological reviews of the Cambridge Philosophical Society* 2016, 91 (2), 452-68.
64. Han, H.-S.; Kang, G., et al., Regulation of glucose metabolism from a liver-centric perspective. *Experimental & Molecular Medicine* 2016, 48 (3), e218-e218.
65. Xia, C.; Li, M., et al., Redox-responsive nanoassembly restrained myeloid-derived suppressor cells recruitment through autophagy-involved lactate dehydrogenase A silencing for enhanced cancer immunochemotherapy. *J Control Release* 2021, 335, 557-574.
66. Gwangwa, M. V.; Joubert, A. M., et al., Crosstalk between the Warburg effect, redox regulation and autophagy induction in tumourigenesis. *Cellular & molecular biology letters* 2018, 23, 20.
67. Huang, T.; Song, X., et al., Autophagy and Hallmarks of Cancer. *Critical reviews in oncogenesis* 2018, 23 (5-6), 247-267.
68. Peng, X.; Gong, F., et al., Autophagy promotes paclitaxel resistance of cervical cancer cells: involvement of Warburg effect activated hypoxia-induced factor 1- α -mediated signaling. *Cell death & disease* 2014, 5 (8), e1367-e1367.
69. Guido, C.; Whitaker-Menezes, D., et al., Metabolic reprogramming of cancer-associated fibroblasts by TGF- β drives tumor growth: connecting TGF- β signaling with "Warburg-like" cancer metabolism and L-lactate production. *Cell cycle* 2012, 11 (16), 3019-3035.
70. Ward, P. S.; Thompson, C. B., Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. *Cancer cell* 2012, 21 (3), 297-308.
71. Luo, X.; Cheng, C., et al., Emerging roles of lipid metabolism in cancer metastasis. *Molecular Cancer* 2017, 16 (1), 76.
72. Yang, M.; Zhang, Y., et al., Autophagic Regulation of Lipid Homeostasis in Cardiometabolic Syndrome. *Frontiers in Cardiovascular Medicine* 2018, 5.
73. Xie, Y.; Li, J., et al., Interplay Between Lipid Metabolism and Autophagy. *Front Cell Dev Biol* 2020, 8, 431-431.
74. Yang, M.; Zhang, Y., et al., Autophagic Regulation of Lipid Homeostasis in Cardiometabolic Syndrome. *Frontiers in cardiovascular medicine* 2018, 5, 38-38.
75. Jaishy, B.; Abel, E. D., Lipids, lysosomes, and autophagy. *Journal of Lipid Research* 2016, 57 (9), 1619-1635.
76. Dall'Armi, C.; Devereaux, Kelly A., et al., The Role of Lipids in the Control of Autophagy. *Current Biology* 2013, 23 (1), R33-R45.
77. Su, T.; Li, X., et al., Autophagy: An Intracellular Degradation Pathway Regulating Plant Survival and Stress Response. *Frontiers in Plant Science* 2020, 11.
78. Soto-Avellaneda, A.; Morrison, B. E., Signaling and other functions of lipids in autophagy: a review. *Lipids in Health and Disease* 2020, 19 (1), 214.
79. Zhang, S.; Peng, X., et al., The regulation, function, and role of lipophagy, a form of selective autophagy, in metabolic disorders. *Cell Death & Disease* 2022, 13 (2), 132.
80. Paik, S.; Jo, E.-K., An Interplay Between Autophagy and Immunometabolism for Host Defense Against Mycobacterial Infection. *Frontiers in Immunology* 2020, 11.
81. Paik, S.; Jo, E.-K., An Interplay Between Autophagy and Immunometabolism for Host Defense Against Mycobacterial Infection. *Frontiers in immunology* 2020, 11, 603951-603951.

82. Lahiri, V.; Hawkins, W. D., et al., Watch What You (Self-) Eat: Autophagic Mechanisms that Modulate Metabolism. *Cell Metabolism* 2019, 29 (4), 803-826.
83. Shan, W.; Zhou, Y., et al., The development of small-molecule inhibitors targeting hexokinase 2. *Drug Discov Today* 2022.
84. Du, D.; Liu, C., et al., Metabolic dysregulation and emerging therapeutical targets for hepatocellular carcinoma. *Acta Pharm Sin B* 2022, 12 (2), 558-580.
85. Halestrap, A. P.; Pereira, G. C., et al., The role of hexokinase in cardioprotection - mechanism and potential for translation. *Br J Pharmacol* 2015, 172 (8), 2085-100.
86. DeWaal, D.; Nogueira, V., et al., Hexokinase-2 depletion inhibits glycolysis and induces oxidative phosphorylation in hepatocellular carcinoma and sensitizes to metformin. *Nature communications* 2018, 9 (1), 1-14.
87. Palmieri, D.; Fitzgerald, D., et al., Analyses of resected human brain metastases of breast cancer reveal the association between up-regulation of hexokinase 2 and poor prognosis. *Molecular Cancer Research* 2009, 7 (9), 1438-1445.
88. Zhang, X.-Y.; Zhang, M., et al., Hexokinase 2 confers resistance to cisplatin in ovarian cancer cells by enhancing cisplatin-induced autophagy. *The international journal of biochemistry & cell biology* 2018, 95, 9-16.
89. Wu, J.; Zhang, X., et al., Licochalcone A suppresses hexokinase 2-mediated tumor glycolysis in gastric cancer via downregulation of the Akt signaling pathway. *Oncology reports* 2018, 39 (3), 1181-1190.
90. Xu, D.; Jin, J., et al., Chrysin inhibited tumor glycolysis and induced apoptosis in hepatocellular carcinoma by targeting hexokinase-2. *Journal of Experimental & Clinical Cancer Research* 2017, 36 (1), 1-11.
91. Chen, J.; Zhang, S., et al., Hexokinase 2 overexpression promotes the proliferation and survival of laryngeal squamous cell carcinoma. *Tumor Biology* 2014, 35 (4), 3743-3753.
92. Yoshino, H.; Enokida, H., et al., Tumor-suppressive micro RNA-143/145 cluster targets hexokinase-2 in renal cell carcinoma. *Cancer science* 2013, 104 (12), 1567-1574.
93. Arundhati, J. R. D.; Mathur, S. R., et al., Metabolic changes in triple negative breast cancer-focus on aerobic glycolysis. *Mol Biol Rep* 2021, 48 (5), 4733-4745.
94. Mathupala, S.; Ko, Y. a., et al., Hexokinase II: cancer's double-edged sword acting as both facilitator and gatekeeper of malignancy when bound to mitochondria. *Oncogene* 2006, 25 (34), 4777-4786.
95. Fan, K.; Fan, Z., et al., Hexokinase 2 dimerization and interaction with voltage-dependent anion channel promoted resistance to cell apoptosis induced by gemcitabine in pancreatic cancer. *Cancer medicine* 2019, 8 (13), 5903-5915.
96. Gu, J. J.; Singh, A., et al., Up-regulation of hexokinase II contributes to rituximab-chemotherapy resistance and is a clinically relevant target for therapeutic development. *Oncotarget* 2018, 9 (3), 4020.
97. Suh, D. H.; Kim, M. A., et al., Association of overexpression of hexokinase II with chemoresistance in epithelial ovarian cancer. *Clinical and experimental medicine* 2014, 14 (3), 345-353.
98. Varghese, E.; Samuel, S. M., et al., Targeting Glucose Metabolism to Overcome Resistance to Anticancer Chemotherapy in Breast Cancer. *Cancers (Basel)* 2020, 12 (8).
99. Patra, K. C.; Wang, Q., et al., Hexokinase 2 is required for tumor initiation and maintenance and its systemic deletion is therapeutic in mouse models of cancer. *Cancer cell* 2013, 24 (2), 213-228.
100. Gregersen, L. H.; Jacobsen, A., et al., MicroRNA-143 down-regulates Hexokinase 2 in colon cancer cells. *BMC cancer* 2012, 12 (1), 1-10.
101. Jiang, S.; Zhang, L. F., et al., A novel miR-155/miR-143 cascade controls glycolysis by regulating hexokinase 2 in breast cancer cells. *The EMBO journal* 2012, 31 (8), 1985-1998.
102. Kojima, S.; Enokida, H., et al., The tumor-suppressive microRNA-143/145 cluster inhibits cell migration and invasion by targeting GOLM1 in prostate cancer. *Journal of human genetics* 2014, 59 (2), 78-87.
103. Tan, V. P.; Miyamoto, S., HK2/hexokinase-II integrates glycolysis and autophagy to confer cellular protection. *Autophagy* 2015, 11 (6), 963-964.
104. Pilkis, S. J.; Claus, T. H., et al., 6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase: a metabolic signaling enzyme. *Annu Rev Biochem* 1995, 64, 799-835.
105. El-Maghrabi, M. R.; Noto, F., et al., 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase: suiting structure to need, in a family of tissue-specific enzymes. *Curr Opin Clin Nutr Metab Care* 2001, 4 (5), 411-8.
106. Okar, D. A.; Manzano, A., et al., PFK-2/FBPase-2: maker and breaker of the essential biofactor fructose-2,6-bisphosphate. *Trends in biochemical sciences* 2001, 26 (1), 30-5.
107. O'Neal, J.; Clem, A., et al., Inhibition of 6-phosphofructo-2-kinase (PFKFB3) suppresses glucose metabolism and the growth of HER2+ breast cancer. *Breast cancer research and treatment* 2016, 160 (1), 29-40.
108. Imbert-Fernandez, Y.; Clem, B. F., et al., Estradiol stimulates glucose metabolism via 6-phosphofructo-2-kinase (PFKFB3). *Journal of Biological Chemistry* 2014, 289 (13), 9440-9448.
109. Novellasdemunt, L.; Obach, M., et al., Progestins activate 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 3 (PFKFB3) in breast cancer cells. *Biochemical Journal* 2012, 442 (2), 345-356.

110. Dasgupta, S.; Rajapakshe, K., et al., Metabolic enzyme PFKFB4 activates transcriptional coactivator SRC-3 to drive breast cancer. *Nature* 2018, 556 (7700), 249-254.
111. Gao, R.; Liu, Y., et al., PFKFB4 promotes breast cancer metastasis via induction of hyaluronan production in a p38-dependent manner. *Cellular Physiology and Biochemistry* 2018, 50 (6), 2108-2123.
112. Yao, L.; Wang, L., et al., High expression of metabolic enzyme PFKFB4 is associated with poor prognosis of operable breast cancer. *Cancer cell international* 2019, 19 (1), 1-8.
113. Gao, R.; Li, D., et al., CD44ICD promotes breast cancer stemness via PFKFB4-mediated glucose metabolism. *Theranostics* 2018, 8 (22), 6248.
114. Hu, K. Y.; Wang, D. G., et al., Targeting of MCT1 and PFKFB3 influences cell proliferation and apoptosis in bladder cancer by altering the tumor microenvironment. *Oncology reports* 2016, 36 (2), 945-951.
115. Yun, S. J.; Jo, S.-W., et al. In PFKFB4 as a prognostic marker in non-muscle-invasive bladder cancer, *Urologic Oncology: Seminars and Original Investigations*, Elsevier: 2012; pp 893-899.
116. Bobarykina, A. Y.; Minchenko, D. O., et al., Hypoxic regulation of PFKFB-3 and PFKFB-4 gene expression in gastric and pancreatic cancer cell lines and expression of PFKFB genes in gastric cancers. *Acta Biochimica Polonica* 2006, 53 (4), 789-799.
117. Minchenko, O. H.; Tsuchihara, K., et al., Mechanisms of regulation of PFKFB expression in pancreatic and gastric cancer cells. *World journal of gastroenterology: WJG* 2014, 20 (38), 13705.
118. Bolaños, J. P., Adapting glycolysis to cancer cell proliferation: the MAPK pathway focuses on PFKFB3. *Biochemical Journal* 2013, 452 (3), e7-e9.
119. Klarer, A. C.; O'Neal, J., et al., Inhibition of 6-phosphofructo-2-kinase (PFKFB3) induces autophagy as a survival mechanism. *Cancer & metabolism* 2014, 2 (1), 1-14.
120. Strohecker, A. M.; Joshi, S., et al., Identification of 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase as a novel autophagy regulator by high content shRNA screening. *Oncogene* 2015, 34 (45), 5662-5676.
121. Yang, Z.; Goronzy, J. J., et al., The glycolytic enzyme PFKFB3/phosphofructokinase regulates autophagy. *Autophagy* 2014, 10 (2), 382-383.
122. Ripple, M. O.; Wilding, G., Alteration of glyceraldehyde-3-phosphate dehydrogenase activity and messenger RNA content by androgen in human prostate carcinoma cells. *Cancer research* 1995, 55 (19), 4234-4236.
123. Marcucci, F.; Rumio, C., Tumor Cell Glycolysis-At the Crossroad of Epithelial-Mesenchymal Transition and Autophagy. *Cells* 2022, 11 (6).
124. Butera, G.; Mullappilly, N., et al., Regulation of Autophagy by Nuclear GAPDH and Its Aggregates in Cancer and Neurodegenerative Disorders. *Int J Mol Sci* 2019, 20 (9).
125. Chang, C.; Su, H., et al., AMPK-dependent phosphorylation of GAPDH triggers Sirt1 activation and is necessary for autophagy upon glucose starvation. *Molecular cell* 2015, 60 (6), 930-940.
126. Tokunaga, K.; Nakamura, Y., et al., Enhanced expression of a glyceraldehyde-3-phosphate dehydrogenase gene in human lung cancers. *Cancer research* 1987, 47 (21), 5616-5619.
127. Phadke, M.; Krynetskaia, N., et al., Accelerated cellular senescence phenotype of GAPDH-depleted human lung carcinoma cells. *Biochemical and biophysical research communications* 2011, 411 (2), 409-415.
128. Huang, Q.; Lan, F., et al., Akt2 kinase suppresses glyceraldehyde-3-phosphate dehydrogenase (GAPDH)-mediated apoptosis in ovarian cancer cells via phosphorylating GAPDH at threonine 237 and decreasing its nuclear translocation. *Journal of Biological Chemistry* 2011, 286 (49), 42211-42220.
129. Harada, N.; Yasunaga, R., et al., Glyceraldehyde-3-phosphate dehydrogenase enhances transcriptional activity of androgen receptor in prostate cancer cells. *Journal of Biological Chemistry* 2007, 282 (31), 22651-22661.
130. Correa, C.; Bertollo, C., et al., Glyceraldehyde-3-phosphate dehydrogenase as a surface associated antigen on human breast cancer cell lines MACL-1 and MGSO-3. *Oncology reports* 2010, 24 (3), 677-685.
131. Pacchiana, R.; Mullappilly, N., et al., 3-Bromo-Isoxazoline Derivatives Inhibit GAPDH Enzyme in PDAC Cells Triggering Autophagy and Apoptotic Cell Death. *Cancers (Basel)* 2022, 14 (13).
132. Dando, I.; Pacchiana, R., et al., UCP2 inhibition induces ROS/Akt/mTOR axis: role of GAPDH nuclear translocation in genipin/everolimus anticancer synergism. *Free Radical Biology and Medicine* 2017, 113, 176-189.
133. Wang, S.; Jiang, B., et al., Insulin and mTOR pathway regulate HDAC3-mediated deacetylation and activation of PGK1. *PLoS Biol* 2015, 13 (9), e1002243.
134. Rojas-Pirela, M.; Andrade-Alvarez, D., et al., Phosphoglycerate kinase: structural aspects and functions, with special emphasis on the enzyme from Kinetoplastea. *Open Biol* 2020, 10 (11), 200302.
135. Qian, X.; Li, X., et al., Phosphoglycerate kinase 1 phosphorylates Beclin1 to induce autophagy. *Molecular cell* 2017, 65 (5), 917-931. e6.
136. Zhang, T.; Wang, Y., et al., PGK1 represses autophagy-mediated cell death to promote the proliferation of liver cancer cells by phosphorylating PRAS40. *Cell Death Dis* 2022, 13 (1), 68.
137. Altenberg, B. a.; Greulich, K., Genes of glycolysis are ubiquitously overexpressed in 24 cancer classes. *Genomics* 2004, 84 (6), 1014-1020.

138. Hardt, P.; Mazurek, S., et al., Faecal tumour M2 pyruvate kinase: a new, sensitive screening tool for colorectal cancer. *British journal of cancer* 2004, 91 (5), 980-984.
139. Verma, H.; Cholia, R. P., et al., A short review on cross-link between pyruvate kinase (PKM2) and Glioblastoma Multiforme. *Metab Brain Dis* 2021, 36 (5), 751-765.
140. Dey, P.; Kundu, A., et al., PKM2 Knockdown Induces Autophagic Cell Death via the AKT/mTOR Pathway in Human Prostate Cancer Cells. 2019.
141. Lin, M., Pyruvate Kinase Isoform M2 Influences Autophagy and Related Processes in Hepatocellular Carcinoma Cells. 2018.
142. Tamada, M.; Suematsu, M., et al., Pyruvate kinase M2: multiple faces for conferring benefits on cancer cells. *Clinical cancer research* 2012, 18 (20), 5554-5561.
143. Christofk, H. R.; Vander Heiden, M. G., et al., The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature* 2008, 452 (7184), 230-233.
144. Kumar, Y.; Tapuria, N., et al., Tumour M2-pyruvate kinase: a gastrointestinal cancer marker. *European journal of gastroenterology & hepatology* 2007, 19 (3), 265-276.
145. Lv, L.; Li, D., et al., Acetylation targets the M2 isoform of pyruvate kinase for degradation through chaperone-mediated autophagy and promotes tumor growth. *Molecular cell* 2011, 42 (6), 719-730.
146. Xu, Q.; Wu, N., et al., Inhibition of PTP1B blocks pancreatic cancer progression by targeting the PKM2/AMPK/mTORC1 pathway. *Cell death & disease* 2019, 10 (12), 1-15.
147. Wang, L.; Yang, L., et al., Glycolytic enzyme PKM2 mediates autophagic activation to promote cell survival in NPM1-mutated leukemia. *International journal of biological sciences* 2019, 15 (4), 882.
148. Yu, Z.; Wang, D., et al., PKM2 promotes cell metastasis and inhibits autophagy via the JAK/STAT3 pathway in hepatocellular carcinoma. *Mol Cell Biochem* 2021, 476 (5), 2001-2010.
149. DM, D.; TL, G., et al., LACTIC DEHYDROGENASES: FUNCTIONS OF THE TWO TYPES RATES OF SYNTHESIS OF THE TWO MAJOR FORMS CAN BE CORRELATED WITH METABOLIC DIFFERENTIATION. *Science (New York, NY)* 1964, 143 (3609), 929-933.
150. Valvona, C. J.; Fillmore, H. L., et al., The regulation and function of lactate dehydrogenase A: therapeutic potential in brain tumor. *Brain pathology* 2016, 26 (1), 3-17.
151. Gordon, J. S.; Wood, C. T., et al., Clinical implications of LDH isoenzymes in hemolysis and continuous-flow left ventricular assist device-induced thrombosis. *Artif Organs* 2020, 44 (3), 231-238.
152. Sheng, S. L.; Liu, J. J., et al., Knockdown of lactate dehydrogenase A suppresses tumor growth and metastasis of human hepatocellular carcinoma. *The FEBS journal* 2012, 279 (20), 3898-3910.
153. Zhou, S.; Min, Z., et al., miR-199a-3p/Sp1/LDHA axis controls aerobic glycolysis in testicular tumor cells. *International journal of molecular medicine* 2018, 42 (4), 2163-2174.
154. Guddeti, R. K.; Bali, P., et al., MTA1 coregulator regulates LDHA expression and function in breast cancer. *Biochemical and biophysical research communications* 2019, 520 (1), 54-59.
155. Huang, X.; Li, X., et al., High expressions of LDHA and AMPK as prognostic biomarkers for breast cancer. *The Breast* 2016, 30, 39-46.
156. Yang, Y.; Su, D., et al., Different effects of LDH-A inhibition by oxamate in non-small cell lung cancer cells. *Oncotarget* 2014, 5 (23), 11886.
157. Das, C. K.; Parekh, A., et al., Lactate dehydrogenase A regulates autophagy and tamoxifen resistance in breast cancer. *Biochim Biophys Acta Mol Cell Res* 2019, 1866 (6), 1004-1018.
158. Brisson, L.; Bański, P., et al., Lactate dehydrogenase B controls lysosome activity and autophagy in cancer. *Cancer Cell* 2016, 30 (3), 418-431.
159. Pilon-Thomas, S.; Kodumudi, K. N., et al., Neutralization of tumor acidity improves antitumor responses to immunotherapy. *Cancer research* 2016, 76 (6), 1381-1390.
160. de la Cruz-López, K. G.; Castro-Muñoz, L. J., et al., Lactate in the regulation of tumor microenvironment and therapeutic approaches. *Frontiers in oncology* 2019, 9, 1143.
161. Rizwan, A.; Serganova, I., et al., Relationships between LDH-A, lactate, and metastases in 4T1 breast tumors. *Clinical Cancer Research* 2013, 19 (18), 5158-5169.
162. Chen, P.; Zuo, H., et al., Gpr132 sensing of lactate mediates tumor-macrophage interplay to promote breast cancer metastasis. *Proceedings of the National Academy of Sciences* 2017, 114 (3), 580-585.
163. Végran, F.; Boidot, R., et al., Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF- κ B/IL-8 pathway that drives tumor angiogenesis. *Cancer research* 2011, 71 (7), 2550-2560.
164. Sonveaux, P.; Copetti, T., et al., Targeting the lactate transporter MCT1 in endothelial cells inhibits lactate-induced HIF-1 activation and tumor angiogenesis. *PloS one* 2012, 7 (3), e33418.
165. Lu, H.; Dalgard, C. L., et al., Reversible inactivation of HIF-1 prolyl hydroxylases allows cell metabolism to control basal HIF-1. *Journal of Biological Chemistry* 2005, 280 (51), 41928-41939.
166. Martínez-Zaguián, R.; Seftor, E. A., et al., Acidic pH enhances the invasive behavior of human melanoma cells. *Clinical & experimental metastasis* 1996, 14 (2), 176-186.
167. Calcinotto, A.; Filipazzi, P., et al., Modulation of microenvironment acidity reverses anergy in human and murine tumor-infiltrating T lymphocytes. *Cancer research* 2012, 72 (11), 2746-2756.

168. Jones, R.; Morris, M., Monocarboxylate transporters: therapeutic targets and prognostic factors in disease. *Clinical Pharmacology & Therapeutics* 2016, 100 (5), 454-463.
169. Garcia, C. K.; Goldstein, J. L., et al., Molecular characterization of a membrane transporter for lactate, pyruvate, and other monocarboxylates: implications for the Cori cycle. *Cell* 1994, 76 (5), 865-873.
170. Pinheiro, C.; Albergaria, A., et al., Monocarboxylate transporter 1 is up-regulated in basal-like breast carcinoma. *Histopathology* 2010, 56 (7), 860-867.
171. Pinheiro, C.; Longatto-Filho, A., et al., Increasing expression of monocarboxylate transporters 1 and 4 along progression to invasive cervical carcinoma. *International Journal of Gynecological Pathology* 2008, 27 (4), 568-574.
172. Pinheiro, C.; Penna, V., et al., Characterization of monocarboxylate transporters (MCTs) expression in soft tissue sarcomas: distinct prognostic impact of MCT1 sub-cellular localization. *Journal of translational medicine* 2014, 12 (1), 1-11.
173. Zhao, Z.; Wu, M.-s., et al., Downregulation of MCT1 inhibits tumor growth, metastasis and enhances chemotherapeutic efficacy in osteosarcoma through regulation of the NF- κ B pathway. *Cancer letters* 2014, 342 (1), 150-158.
174. Pinheiro, C.; Longatto-Filho, A., et al., Monocarboxylate transporters 1 and 4 are associated with CD147 in cervical carcinoma. *Disease markers* 2009, 26 (3), 97-103.
175. Jin, P.; Jiang, J., et al., MCT1 relieves osimertinib-induced CRC suppression by promoting autophagy through the LKB1/AMPK signaling. *Cell death & disease* 2019, 10 (8), 1-15.
176. Long, Y.; Gao, Z., et al., Downregulation of MCT 4 for lactate exchange promotes the cytotoxicity of NK cells in breast carcinoma. *Cancer medicine* 2018, 7 (9), 4690-4700.
177. Kierans, S. J.; Taylor, C. T., Regulation of glycolysis by the hypoxia-inducible factor (HIF): implications for cellular physiology. *J Physiol* 2021, 599 (1), 23-37.
178. Mazure, N. M.; Pouyssegur, J., Hypoxia-induced autophagy: cell death or cell survival? *Current opinion in cell biology* 2010, 22 (2), 177-180.
179. Noman, M. Z.; Janji, B., et al., Hypoxia-induced autophagy: a new player in cancer immunotherapy? *Autophagy* 2012, 8 (4), 704-706.
180. Papandreou, I.; Lim, A., et al., Hypoxia signals autophagy in tumor cells via AMPK activity, independent of HIF-1, BNIP3, and BNIP3L. *Cell Death & Differentiation* 2008, 15 (10), 1572-1581.
181. de Mello, N. P.; Orellana, A. M., et al., Insulin and autophagy in neurodegeneration. *Frontiers in neuroscience* 2019, 13, 491.
182. Fu, D.; He, C., et al., PGK1 is a Potential Survival Biomarker and Invasion Promoter by Regulating the HIF-1 α -Mediated Epithelial-Mesenchymal Transition Process in Breast Cancer. *Cellular Physiology and Biochemistry* 2018, 51 (5), 2434-2444.
183. Sugiyama, T.; Taniguchi, K., et al., MiR-133b inhibits growth of human gastric cancer cells by silencing pyruvate kinase muscle-splicer polypyrimidine tract-binding protein 1. *Cancer science* 2016, 107 (12), 1767-1775.
184. Das, C. K.; Parekh, A., et al., Lactate dehydrogenase A regulates autophagy and tamoxifen resistance in breast cancer. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 2019, 1866 (6), 1004-1018.
185. Shi, L.; Yan, H., et al., SIRT 5-mediated deacetylation of LDHB promotes autophagy and tumorigenesis in colorectal cancer. *Molecular oncology* 2019, 13 (2), 358-375.
186. Shen, Y.; Liu, Y., et al., LincRNA-p21 knockdown enhances radiosensitivity of hypoxic tumor cells by reducing autophagy through HIF-1/Akt/mTOR/P70S6K pathway. *Experimental cell research* 2017, 358 (2), 188-198.
187. Talks, K. L.; Turley, H., et al., The expression and distribution of the hypoxia-inducible factors HIF-1 α and HIF-2 α in normal human tissues, cancers, and tumor-associated macrophages. *The American journal of pathology* 2000, 157 (2), 411-421.
188. Wang, C. W., Lipid droplets, lipophagy, and beyond. *Biochimica et biophysica acta* 2016, 1861 (8 Pt B), 793-805.
189. Jaishy, B.; Abel, E. D., Lipids, lysosomes, and autophagy. *Journal of lipid research* 2016, 57 (9), 1619-35.
190. Efeyan, A.; Comb, W. C., et al., Nutrient-sensing mechanisms and pathways. *Nature* 2015, 517 (7534), 302-10.
191. Ward, C.; Martinez-Lopez, N., et al., Autophagy, lipophagy and lysosomal lipid storage disorders. *Biochimica et biophysica acta* 2016, 1861 (4), 269-84.
192. Schulze, R. J.; Sathyanarayan, A., et al., Breaking fat: The regulation and mechanisms of lipophagy. *Biochimica et biophysica acta. Molecular and cell biology of lipids* 2017, 1862 (10 Pt B), 1178-1187.
193. Martinez-Lopez, N.; Singh, R., Autophagy and Lipid Droplets in the Liver. *Annual review of nutrition* 2015, 35, 215-37.
194. Fafián-Labora, J.; Carpintero-Fernández, P., et al., FASN activity is important for the initial stages of the induction of senescence. *Cell Death Dis* 2019, 10 (4), 318.

195. Humbert, M.; Seiler, K., et al., Autophagy-mediated degradation of Fatty Acid Synthase (FASN) facilitates ATRA-induced granulocytic differentiation of acute myeloid leukemia (AML) cells. *bioRxiv* 2020, 2020.01.29.924555.
196. Palmieri, M.; Impey, S., et al., Characterization of the CLEAR network reveals an integrated control of cellular clearance pathways. *Human Molecular Genetics* 2011, 20 (19), 3852-3866.
197. Wang, H.; Luo, Q. F., et al., Positive feedback regulation between Akt phosphorylation and fatty acid synthase expression in osteosarcoma. *Int J Mol Med* 2014, 33 (3), 633-9.
198. Zaytseva, Y. Y.; Harris, J. W., et al., Increased expression of fatty acid synthase provides a survival advantage to colorectal cancer cells via upregulation of cellular respiration. *Oncotarget* 2015, 6 (22), 18891-904.
199. Alizadeh, J.; Zeki, A. A., et al., Mevalonate Cascade Inhibition by Simvastatin Induces the Intrinsic Apoptosis Pathway via Depletion of Isoprenoids in Tumor Cells. *Scientific reports* 2017, 7, 44841-44841.
200. Ahmadi, M.; Amiri, S., et al., Pleiotropic effects of statins: A focus on cancer. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 2020, 1866 (12), 165968.
201. Peymani, P.; Dehesh, T., et al., Statins in patients with COVID-19: a retrospective cohort study in Iranian COVID-19 patients. *Transl Med Commun* 2021, 6 (1), 3.
202. Ghavami, S.; Sharma, P., et al., Airway mesenchymal cell death by mevalonate cascade inhibition: integration of autophagy, unfolded protein response and apoptosis focusing on Bcl2 family proteins. *Biochimica et biophysica acta* 2014, 1843 (7), 1259-71.
203. Vilimanovich, U.; Bosnjak, M., et al., Statin-mediated inhibition of cholesterol synthesis induces cytoprotective autophagy in human leukemic cells. *European Journal of Pharmacology* 2015, 765, 415-428.
204. Guo, J. Y.; Karsli-Uzunbas, G., et al., Autophagy suppresses progression of K-ras-induced lung tumors to oncocytoomas and maintains lipid homeostasis. *Genes & development* 2013, 27 (13), 1447-61.
205. Wang, H. J.; Park, J. Y., et al., Chronic HMGCR/HMG-CoA reductase inhibitor treatment contributes to dysglycemia by upregulating hepatic gluconeogenesis through autophagy induction. *Autophagy* 2015, 11 (11), 2089-2101.
206. Parikh, A.; Childress, C., et al., Statin-induced autophagy by inhibition of geranylgeranyl biosynthesis in prostate cancer PC3 cells. *The Prostate* 2010, 70 (9), 971-81.
207. Araki, M.; Motojima, K., Hydrophobic statins induce autophagy in cultured human rhabdomyosarcoma cells. *Biochemical and Biophysical Research Communications* 2008, 367 (2), 462-467.
208. Araki, M.; Maeda, M., et al., Hydrophobic statins induce autophagy and cell death in human rhabdomyosarcoma cells by depleting geranylgeranyl diphosphate. *European Journal of Pharmacology* 2012, 674 (2), 95-103.
209. Emami, A.; Shojaei, S., et al., Mechanisms of simvastatin myotoxicity: The role of autophagy flux inhibition. *Eur J Pharmacol* 2019, 862, 172616.
210. Hou, H.; Zhang, Y., et al., Inhibitors of phosphatidylinositol 3'-kinases promote mitotic cell death in HeLa cells. *PLoS One* 2012, 7 (4), e35665.
211. Khanzada, U. K.; Pardo, O. E., et al., Potent inhibition of small-cell lung cancer cell growth by simvastatin reveals selective functions of Ras isoforms in growth factor signalling. *Oncogene* 2006, 25 (6), 877-887.
212. Calabro, A.; Tai, J., et al., In-vitro synergism of m-TOR inhibitors, statins, and classical chemotherapy: potential implications in acute leukemia. *Anti-cancer drugs* 2008, 19 (7), 705-12.
213. Cemeus, C.; Zhao, T. T., et al., Lovastatin enhances gefitinib activity in glioblastoma cells irrespective of EGFRvIII and PTEN status. *Journal of Neuro-Oncology* 2008, 90 (1), 9-17.
214. Martirosyan, A.; Clendening, J. W., et al., Lovastatin induces apoptosis of ovarian cancer cells and synergizes with doxorubicin: potential therapeutic relevance. *BMC Cancer* 2010, 10, 103.
215. Cannavo, A.; Liccardo, D., et al., Sphingosine Kinases and Sphingosine 1-Phosphate Receptors: Signaling and Actions in the Cardiovascular System. *Frontiers in pharmacology* 2017, 8, 556-556.
216. Long, J.; Xie, Y., et al., SphK1 promotes tumor cell migration and invasion in colorectal cancer. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine* 2016, 37 (5), 6831-6.
217. Almejún, M. B.; Borge, M., et al., Sphingosine kinase 1 participates in the activation, proliferation and survival of chronic lymphocytic leukemia cells. *Haematologica* 2017, 102 (7), e257-e260.
218. Li, J.; Guan, H. Y., et al., Clinical significance of sphingosine kinase-1 expression in human astrocytomas progression and overall patient survival. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2008, 14 (21), 6996-7003.
219. Kawamori, T.; Kaneshiro, T., et al., Role for sphingosine kinase 1 in colon carcinogenesis. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 2009, 23 (2), 405-14.
220. Pchejetski, D.; Doumerc, N., et al., Chemosensitizing effects of sphingosine kinase-1 inhibition in prostate cancer cell and animal models. *Molecular Cancer Therapeutics* 2008, 7 (7), 1836.

221. Akao, Y.; Banno, Y., et al., High expression of sphingosine kinase 1 and S1P receptors in chemotherapy-resistant prostate cancer PC3 cells and their camptothecin-induced up-regulation. *Biochem Biophys Res Commun* 2006, 342 (4), 1284-90.
222. Bao, M.; Chen, Z., et al., Sphingosine kinase 1 promotes tumour cell migration and invasion via the S1P/EDG1 axis in hepatocellular carcinoma. *Liver international : official journal of the International Association for the Study of the Liver* 2012, 32 (2), 331-8.
223. Moruno Manchon, J. F.; Uzor, N. E., et al., SPHK1/sphingosine kinase 1-mediated autophagy differs between neurons and SH-SY5Y neuroblastoma cells. *Autophagy* 2016, 12 (8), 1418-24.
224. Lavieu, G.; Scarlatti, F., et al., Regulation of autophagy by sphingosine kinase 1 and its role in cell survival during nutrient starvation. *The Journal of biological chemistry* 2006, 281 (13), 8518-27.
225. Xu, C.; Zhang, W., et al., Activation of the SphK1/ERK/p-ERK pathway promotes autophagy in colon cancer cells. *Oncol Lett* 2018, 15 (6), 9719-9724.
226. Liu, H.; Ma, Y., et al., SPHK1 (sphingosine kinase 1) induces epithelial-mesenchymal transition by promoting the autophagy-linked lysosomal degradation of CDH1/E-cadherin in hepatoma cells. *Autophagy* 2017, 13 (5), 900-913.
227. Yin, S.; Miao, Z., et al., SPHK1-induced autophagy in peritoneal mesothelial cell enhances gastric cancer peritoneal dissemination. *Cancer Medicine* 2019, 8 (4), 1731-1743.
228. Jeppesen, J.; Mogensen, M., et al., FAT/CD36 is localized in sarcolemma and in vesicle-like structures in subsarcolemma regions but not in mitochondria. *Journal of lipid research* 2010, 51 (6), 1504-1512.
229. Li, Y.; Yang, P., et al., CD36 plays a negative role in the regulation of lipophagy in hepatocytes through an AMPK-dependent pathway. *Journal of lipid research* 2019, 60 (4), 844-855.
230. Su, W.; Frohman, M. A., Chapter 144 - Phospholipase D. In *Handbook of Cell Signaling (Second Edition)*, Bradshaw, R. A.; Dennis, E. A., Eds. Academic Press: San Diego, 2010; pp 1167-1176.
231. Foster, D. A., Phosphatidic acid signaling to mTOR: signals for the survival of human cancer cells. *Biochimica et biophysica acta* 2009, 1791 (9), 949-955.
232. Fang, Y.; Vilella-Bach, M., et al., Phosphatidic acid-mediated mitogenic activation of mTOR signaling. *Science (New York, N.Y.)* 2001, 294 (5548), 1942-5.
233. Shahnazari, S.; Yen, W.-L., et al., A Diacylglycerol-Dependent Signaling Pathway Contributes to Regulation of Antibacterial Autophagy. *Cell Host & Microbe* 2010, 8 (2), 137-146.
234. Genc, G. E.; Hipolito, V. E. B., et al., Lysophosphatidic acid represses autophagy in prostate carcinoma cells. *Biochem Cell Biol* 2019, 97 (4), 387-396.
235. Holland, P.; Knaevelsrud, H., et al., HS1BP3 negatively regulates autophagy by modulation of phosphatidic acid levels. *Nat Commun* 2016, 7, 13889.
236. Carmen, B.; Thierry, L., et al., Regulation of Autophagy by Sphingolipids. *Anti-Cancer Agents in Medicinal Chemistry* 2011, 11 (9), 844-853.
237. Spassieva, S. D.; Mullen, T. D., et al., Disruption of ceramide synthesis by CerS2 down-regulation leads to autophagy and the unfolded protein response. *The Biochemical journal* 2009, 424 (2), 273-83.
238. Pattingre, S.; Bauvy, C., et al., Role of JNK1-dependent Bcl-2 Phosphorylation in Ceramide-induced Macroautophagy. *Journal of Biological Chemistry* 2009, 284 (5), 2719-2728.
239. Lavieu, G.; Scarlatti, F., et al., Regulation of Autophagy by Sphingosine Kinase 1 and Its Role in Cell Survival during Nutrient Starvation. *Journal of Biological Chemistry* 2006, 281 (13), 8518-8527.
240. Pattingre, S.; Bauvy, C., et al., Role of JNK1-dependent Bcl-2 phosphorylation in ceramide-induced macroautophagy. *The Journal of biological chemistry* 2009, 284 (5), 2719-2728.
241. Scarlatti, F.; Bauvy, C., et al., Ceramide-mediated macroautophagy involves inhibition of protein kinase B and up-regulation of beclin 1. *The Journal of biological chemistry* 2004, 279 (18), 18384-91.
242. Guenther, G. G.; Peralta, E. R., et al., Ceramide starves cells to death by downregulating nutrient transporter proteins. *Proc Natl Acad Sci U S A* 2008, 105 (45), 17402-7.
243. Lépine, S.; Allegood, J. C., et al., Sphingosine-1-phosphate phosphohydrolase-1 regulates ER stress-induced autophagy. *Cell death and differentiation* 2011, 18 (2), 350-61.
244. Chang, C. L.; Ho, M. C., et al., S1P(5) is required for sphingosine 1-phosphate-induced autophagy in human prostate cancer PC-3 cells. *American journal of physiology. Cell physiology* 2009, 297 (2), C451-8.
245. Berger, J.; Moller, D. E., The Mechanisms of Action of PPARs. *Annual Review of Medicine* 2002, 53 (1), 409-435.
246. Miyata, K. S.; McCaw, S. E., et al., The peroxisome proliferator-activated receptor interacts with the retinoid X receptor in vivo. *Gene* 1994, 148 (2), 327-330.
247. Bull, A. W.; Steffensen, K. R., et al., Activation of PPAR γ in colon tumor cell lines by oxidized metabolites of linoleic acid, endogenous ligands for PPAR γ . *Carcinogenesis* 2003, 24 (11), 1717-1722.
248. Velkov, T., Interactions between Human Liver Fatty Acid Binding Protein and Peroxisome Proliferator Activated Receptor Selective Drugs. *PPAR Research* 2013, 2013, 938401.
249. Kim, Y. S.; Lee, H.-M., et al., PPAR- α Activation Mediates Innate Host Defense through Induction of TFEB and Lipid Catabolism. *The Journal of Immunology* 2017, 198 (8), 3283-3295.

250. Palomer, X.; Capdevila-Busquets, E., et al., PPAR γ attenuates palmitate-induced endoplasmic reticulum stress and induces autophagic markers in human cardiac cells. *International Journal of Cardiology* 2014, 174 (1), 110-118.
251. Assumpção, J. A. F.; Magalhães, K. G., et al., The role of ppar γ and autophagy in ros production, lipid droplets biogenesis and its involvement with colorectal cancer cells modulation. *Cancer Cell International* 2017, 17 (1), 82.
252. Zhou, J.; Zhang, W., et al., PPAR γ activation induces autophagy in breast cancer cells. *The International Journal of Biochemistry & Cell Biology* 2009, 41 (11), 2334-2342.
253. Bajaj, M.; Suraamornkul, S., et al., Sustained Reduction in Plasma Free Fatty Acid Concentration Improves Insulin Action without Altering Plasma Adipocytokine Levels in Subjects with Strong Family History of Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism* 2004, 89 (9), 4649-4655.
254. Wang, C.-W., Lipid droplet dynamics in budding yeast. *Cellular and Molecular Life Sciences* 2015, 72 (14), 2677-2695.
255. Carta, G.; Murru, E., et al., Palmitic Acid: Physiological Role, Metabolism and Nutritional Implications. *Front Physiol* 2017, 8, 902-902.
256. Tan, S. H.; Shui, G., et al., Induction of Autophagy by Palmitic Acid via Protein Kinase C-mediated Signaling Pathway Independent of mTOR (Mammalian Target of Rapamycin) ^{*}. *Journal of Biological Chemistry* 2012, 287 (18), 14364-14376.
257. Fukui, M.; Kang, K. S., et al., EPA, an omega-3 fatty acid, induces apoptosis in human pancreatic cancer cells: Role of ROS accumulation, caspase-8 activation, and autophagy induction. *Journal of Cellular Biochemistry* 2013, 114 (1), 192-203.
258. Swanson, D.; Block, R., et al., Omega-3 fatty acids EPA and DHA: health benefits throughout life. *Adv Nutr* 2012, 3 (1), 1-7.
259. Krauss-Etschmann, S.; Shadid, R., et al., Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: a European randomized multicenter trial. *The American journal of clinical nutrition* 2007, 85 (5), 1392-400.
260. Neff, L. M.; Culiner, J., et al., Algal docosahexaenoic acid affects plasma lipoprotein particle size distribution in overweight and obese adults. *The Journal of nutrition* 2011, 141 (2), 207-13.
261. Chiu, C. C.; Su, K. P., et al., The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. *Progress in neuro-psychopharmacology & biological psychiatry* 2008, 32 (6), 1538-44.
262. Varela-López, A.; Vera-Ramírez, L., et al., The central role of mitochondria in the relationship between dietary lipids and cancer progression. *Seminars in cancer biology* 2021.
263. Shin, S.; Jing, K., et al., The Omega-3 Polyunsaturated Fatty Acid DHA Induces Simultaneous Apoptosis and Autophagy via Mitochondrial ROS-Mediated Akt-mTOR Signaling in Prostate Cancer Cells Expressing Mutant p53. *BioMed Research International* 2013, 2013, 568671.
264. Yao, Q.-H.; Zhang, X.-C., et al., ω -3 polyunsaturated fatty acids inhibit the proliferation of the lung adenocarcinoma cell line A549 in vitro. *Mol Med Rep* 2014, 9 (2), 401-406.
265. Hsu, H.-C.; Chen, C.-Y., et al., Eicosapentaenoic acid attenuated oxidative stress-induced cardiomyoblast apoptosis by activating adaptive autophagy. *European Journal of Nutrition* 2014, 53 (2), 541-547.
266. Nutrition; Health Lifestyle Study, G., Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: a European randomized multicenter trial. *The American journal of clinical nutrition* 2007, 85 (5), 1392-1400.
267. Jing, K.; Song, K.-S., et al., Docosahexaenoic acid induces autophagy through p53/AMPK/mTOR signaling and promotes apoptosis in human cancer cells harboring wild-type p53. *Autophagy* 2011, 7 (11), 1348-1358.
268. Tasdemir, E.; Maiuri, M. C., et al., Regulation of autophagy by cytoplasmic p53. *Nature Cell Biology* 2008, 10 (6), 676-687.
269. D'Eliseo, D.; Di Renzo, L., et al., Docosahexaenoic acid (DHA) promotes immunogenic apoptosis in human multiple myeloma cells, induces autophagy and inhibits STAT3 in both tumor and dendritic cells. *Genes & cancer* 2017, 8 (1-2), 426-437.
270. Pettersen, K.; Monsen, V. T., et al., DHA-induced stress response in human colon cancer cells – Focus on oxidative stress and autophagy. *Free Radical Biology and Medicine* 2016, 90, 158-172.
271. Kanno, S.-i.; Kurauchi, K., et al., Pifithrin-alpha has a p53-independent cytoprotective effect on docosahexaenoic acid-induced cytotoxicity in human hepatocellular carcinoma HepG2 cells. *Toxicology Letters* 2015, 232 (2), 393-402.
272. Omura, Y., Beneficial effects and side effects of DHEA: true anti-aging and age-promoting effects, as well as anti-cancer and cancer-promoting effects of DHEA evaluated from the effects on the normal and cancer cell telomeres and other parameters. *Acupuncture & electro-therapeutics research* 2005, 30 (3-4), 219-61.
273. Rovito, D.; Giordano, C., et al., Omega-3 PUFA ethanolamides DHEA and EPEA induce autophagy through PPAR γ activation in MCF-7 breast cancer cells. *Journal of cellular physiology* 2013, 228 (6), 1314-22.

274. Alphonse, P. A.; Jones, P. J., Revisiting Human Cholesterol Synthesis and Absorption: The Reciprocity Paradigm and its Key Regulators. *Lipids* 2016, 51 (5), 519-36.
275. Yang, S.-T.; Kreutzberger, A. J. B., et al., The role of cholesterol in membrane fusion. *Chem Phys Lipids* 2016, 199, 136-143.
276. Cerqueira, N. M.; Oliveira, E. F., et al., Cholesterol Biosynthesis: A Mechanistic Overview. *Biochemistry* 2016, 55 (39), 5483-5506.
277. Liao, P.; Hemmerlin, A., et al., The potential of the mevalonate pathway for enhanced isoprenoid production. *Biotechnology advances* 2016, 34 (5), 697-713.
278. Jiang, S.-Y.; Li, H., et al., Discovery of a potent HMG-CoA reductase degrader that eliminates statin-induced reductase accumulation and lowers cholesterol. *Nature Communications* 2018, 9 (1), 5138.
279. Tan, S. H.; Shui, G., et al., Induction of autophagy by palmitic acid via protein kinase C-mediated signaling pathway independent of mTOR (mammalian target of rapamycin). *The Journal of biological chemistry* 2012, 287 (18), 14364-76.
280. Shao, W. Q.; Zhu, W. W., et al., Cholesterol suppresses GOLM1-dependent selective autophagy of RTKs in hepatocellular carcinoma. *Cell Rep* 2022, 39 (3), 110712.
281. Kumar, M.; Irungbam, K., et al., Depletion of membrane cholesterol compromised caspase-8 imparts in autophagy induction and inhibition of cell migration in cancer cells. *Cancer Cell Int* 2018, 18, 23.
282. Sung, H.; Ferlay, J., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021, 71 (3), 209-249.
283. Organization, W. H. World Health Organization. *Cancer* [Internet]. Geneva CH: World Health Organization; . (accessed Septemebr 07 2022).
284. Association., A. L. Lung Cancer Fact Sheet [Internet]. Chicago IL: American Lung Association; 2020.
285. Committee, C. C. S. A., Canadian Cancer Statistics 2018. Canadian Cancer Statistics Advisory Committee: 2018.
286. WHO Classification of Tumours of the Lung, Pleura, Thymus, and Heart. In *WHO Classification of Tumours of the Lung, Pleura, Thymus, and Heart*, Travis, W. D.; Brambilla, E.; Burke, A. P.; Marx, A.; Nicholson, A., G., Eds. WHO: Lyon, France., 2015.
287. Sakamoto, T.; Furukawa, T., et al., A collaborative workflow between pathologists and deep learning for the evaluation of tumour cellularity in lung adenocarcinoma. *Histopathology* 2022, 81 (6), 758-769.
288. Oktay, E.; Oflazoglu, U., et al., The prognostic role of thyroid transcription factor-1 in lung adenocarcinoma. *J Cancer Res Ther* 2020, 16 (4), 737-744.
289. Pao, W.; Girard, N., New driver mutations in non-small-cell lung cancer. *Lancet Oncol* 2011, 12 (2), 175-80.
290. Gennen, K.; Kasmann, L., et al., Prognostic value of PD-L1 expression on tumor cells combined with CD8+ TIL density in patients with locally advanced non-small cell lung cancer treated with concurrent chemoradiotherapy. *Radiat Oncol* 2020, 15 (1), 5.
291. Yang, H.; Shi, J., et al., Prognostic value of PD-L1 expression in combination with CD8(+) TILs density in patients with surgically resected non-small cell lung cancer. *Cancer Med* 2018, 7 (1), 32-45.
292. Wang, A.; Wang, H. Y., et al., The prognostic value of PD-L1 expression for non-small cell lung cancer patients: a meta-analysis. *Eur J Surg Oncol* 2015, 41 (4), 450-6.
293. Daaboul, N.; Nicholas, G., et al., Algorithm for the treatment of advanced or metastatic squamous non-small-cell lung cancer: an evidence-based overview. *Curr Oncol* 2018, 25 (Suppl 1), S77-S85.
294. Umakanthan, S.; Bukelo, M. M., Concise genetic profile of lung carcinoma. *Postgrad Med J* 2021.
295. Alberg, A. J.; Samet, J. M., Epidemiology of lung cancer. *Chest* 2003, 123 (1 Suppl), 21S-49S.
296. Taylor, R.; Najafi, F., et al., Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. *Int J Epidemiol* 2007, 36 (5), 1048-59.
297. Kim, C. H.; Lee, Y. C., et al., Exposure to secondhand tobacco smoke and lung cancer by histological type: a pooled analysis of the International Lung Cancer Consortium (ILCCO). *Int J Cancer* 2014, 135 (8), 1918-30.
298. Darby, S.; Hill, D., et al., Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ* 2005, 330 (7485), 223.
299. Krewski, D.; Lubin, J. H., et al., A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health A* 2006, 69 (7), 533-97.
300. Neuberger, J. S.; Field, R. W., Occupation and lung cancer in nonsmokers. *Rev Environ Health* 2003, 18 (4), 251-67.
301. van Loon, A. J.; Kant, I. J., et al., Occupational exposure to carcinogens and risk of lung cancer: results from The Netherlands cohort study. *Occup Environ Med* 1997, 54 (11), 817-24.
302. Gottschall, E. B., Occupational and environmental thoracic malignancies. *J Thorac Imaging* 2002, 17 (3), 189-97.
303. Hubbard, R.; Venn, A., et al., Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med* 2000, 161 (1), 5-8.

304. Chen, Y. C.; Chen, J. H., et al., Lung adenocarcinoma and human papillomavirus infection. *Cancer* 2004, 101 (6), 1428-36.
305. Kirk, G. D.; Merlo, C., et al., HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* 2007, 45 (1), 103-10.
306. Chaturvedi, A. K.; Pfeiffer, R. M., et al., Elevated risk of lung cancer among people with AIDS. *AIDS* 2007, 21 (2), 207-13.
307. D'Jaen, G. A.; Pantanowitz, L., et al., Human immunodeficiency virus-associated primary lung cancer in the era of highly active antiretroviral therapy: a multi-institutional collaboration. *Clin Lung Cancer* 2010, 11 (6), 396-404.
308. Dziadziuszko, R.; Peters, S., et al., Clinical experience and management of adverse events in patients with advanced ALK-positive non-small-cell lung cancer receiving alectinib. *ESMO Open* 2022, 7 (6), 100612.
309. Sun, R.; Hou, Z., et al., Drug resistance mechanisms and progress in the treatment of EGFR-mutated lung adenocarcinoma. *Oncol Lett* 2022, 24 (5), 408.
310. Lindeman, N. I.; Cagle, P. T., et al., Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013, 8 (7), 823-59.
311. Dower, C. M.; Wills, C. A., et al., Mechanisms and context underlying the role of autophagy in cancer metastasis. *Autophagy* 2018, 14 (7), 1110-1128.
312. Chan, E. Y.; Kir, S., et al., siRNA screening of the kinome identifies ULK1 as a multidomain modulator of autophagy. *The Journal of biological chemistry* 2007, 282 (35), 25464-74.
313. Mleczak, A.; Millar, S., et al., Regulation of autophagosome formation by Rho kinase. *Cell Signal* 2013, 25 (1), 1-11.
314. Gurkar, A. U.; Chu, K., et al., Identification of ROCK1 kinase as a critical regulator of Beclin1-mediated autophagy during metabolic stress. *Nature Communications* 2013, 4, 2189.
315. Belaid, A.; Cerezo, M., et al., Autophagy plays a critical role in the degradation of active RHOA, the control of cell cytokinesis, and genomic stability. *Cancer Res* 2013, 73 (14), 4311-22.
316. Belaid, A.; Ndiaye, P. D., et al., Autophagy and SQSTM1 on the RHOA(d) again: emerging roles of autophagy in the degradation of signaling proteins. *Autophagy* 2014, 10 (2), 201-8.
317. Yoshida, T.; Tsujioka, M., et al., Autophagy suppresses cell migration by degrading GEF-H1, a RhoA GEF. *Oncotarget* 2016, 7 (23), 34420-9.
318. Sanz-Moreno, V.; Gadea, G., et al., Rac activation and inactivation control plasticity of tumor cell movement. *Cell* 2008, 135 (3), 510-523.
319. Fang, K.; Chen, X., et al., Serum-Derived Exosomes-Mediated Circular RNA ARHGAP10 Modulates the Progression of Non-Small Cell Lung Cancer Through the miR-638/FAM83F Axis. *Cancer Biother Radiopharm* 2022, 37 (2), 96-110.
320. Li, P.; Lv, H., et al., ARHGAP6 Promotes Apoptosis and Inhibits Glycolysis in Lung Adenocarcinoma Through STAT3 Signaling Pathway. *Cancer Manag Res* 2020, 12, 9665-9678.
321. Maiuri, M. C.; Le Toumelin, G., et al., Functional and physical interaction between Bcl-X(L) and a BH3-like domain in Beclin-1. *EMBO J* 2007, 26 (10), 2527-39.
322. Erlich, S.; Mizrachy, L., et al., Differential interactions between Beclin 1 and Bcl-2 family members. *Autophagy* 2007, 3 (6), 561-8.
323. Pattingre, S.; Tassa, A., et al., Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. *Cell* 2005, 122 (6), 927-39.
324. Adams, J. M.; Cory, S., The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene* 2007, 26 (9), 1324-37.
325. Amundson, S. A.; Myers, T. G., et al., An informatics approach identifying markers of chemosensitivity in human cancer cell lines. *Cancer Res* 2000, 60 (21), 6101-10.
326. Lindqvist, L. M.; Simon, A. K., et al., Current questions and possible controversies in autophagy. *Cell Death Discov* 2015, 1.
327. Lindqvist, L. M.; Heinlein, M., et al., Prosurvival Bcl-2 family members affect autophagy only indirectly, by inhibiting Bax and Bak. *Proc Natl Acad Sci U S A* 2014, 111 (23), 8512-7.
328. Lindqvist, L. M.; Vaux, D. L., BCL2 and related prosurvival proteins require BAK1 and BAX to affect autophagy. *Autophagy* 2014, 10 (8), 1474-5.
329. Pedro, J. M. B.-S.; Wei, Y., et al., BAX and BAK1 are dispensable for ABT-737-induced dissociation of the BCL2-BECN1 complex and autophagy. *Autophagy* 2015, 11 (3), 452-459.
330. Reljic, B.; Conos, S., et al., BAX-BAK1-independent LC3B lipidation by BH3 mimetics is unrelated to BH3 mimetic activity and has only minimal effects on autophagic flux. *Autophagy* 2016, 12 (7), 1083-93.
331. Hanahan, D., Hallmarks of Cancer: New Dimensions. *Cancer discovery* 2022, 12 (1), 31-46.
332. Hanahan, D.; Weinberg, R. A., Hallmarks of cancer: the next generation. *Cell* 2011, 144 (5), 646-74.
333. Hanahan, D.; Weinberg, R. A., The hallmarks of cancer. *Cell* 2000, 100 (1), 57-70.

334. Hombach-Klonisch, S.; Mehrpour, M., et al., Glioblastoma and chemoresistance to alkylating agents: Involvement of apoptosis, autophagy, and unfolded protein response. *Pharmacol Ther* 2018, 184, 13-41.
335. Laplante, M.; Sabatini, D. M., mTOR signaling in growth control and disease. *Cell* 2012, 149 (2), 274-93.
336. Rao, S.; Tortola, L., et al., A dual role for autophagy in a murine model of lung cancer. *Nat Commun* 2014, 5, 3056.
337. Feng, Z.; Zhang, H., et al., The coordinate regulation of the p53 and mTOR pathways in cells. *Proc Natl Acad Sci U S A* 2005, 102 (23), 8204-9.
338. Shaw, R. J.; Bardeesy, N., et al., The LKB1 tumor suppressor negatively regulates mTOR signaling. *Cancer cell* 2004, 6 (1), 91-99.
339. Shackelford, D. B.; Vasquez, D. S., et al., mTOR and HIF-1 α -mediated tumor metabolism in an LKB1 mouse model of Peutz-Jeghers syndrome. *Proceedings of the National Academy of Sciences* 2009, 106 (27), 11137-11142.
340. Faubert, B.; Vincent, E. E., et al., Loss of the tumor suppressor LKB1 promotes metabolic reprogramming of cancer cells via HIF-1 α . *Proceedings of the National Academy of Sciences* 2014, 111 (7), 2554-2559.
341. Sanchez-Céspedes, M.; Parrella, P., et al., Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. *Cancer research* 2002, 62 (13), 3659-3662.
342. Ding, L.; Getz, G., et al., Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* 2008, 455 (7216), 1069-1075.
343. Momcilovic, M.; Bailey, S. T., et al., Utilizing 18F-FDG PET/CT imaging and quantitative histology to measure dynamic changes in the glucose metabolism in mouse models of lung cancer. *Journal of visualized experiments: JoVE* 2018, (137).
344. Luo, L.-X.; Li, Y., et al., Honokiol induces apoptosis, G1 arrest, and autophagy in KRAS mutant lung cancer cells. *Frontiers in pharmacology* 2017, 8, 199.
345. Kapuy, O.; Makk-Merczel, K., et al., Therapeutic Approach of KRAS Mutant Tumours by the Combination of Pharmacologic Ascorbate and Chloroquine. *Biomolecules* 2021, 11 (5), 652.
346. Morita, M.; Sato, T., et al., PKM1 Confers Metabolic Advantages and Promotes Cell-Autonomous Tumor Cell Growth. *Cancer Cell* 2018, 33 (3), 355-367 e7.
347. Fantin, V. R.; Abraham, R. T., Self-eating limits EGFR-dependent tumor growth. *Cell* 2013, 154 (6), 1184-1186.
348. Ye, M.; Wang, S., et al., Combined inhibitions of glycolysis and AKT/autophagy can overcome resistance to EGFR-targeted therapy of lung cancer. *Journal of Cancer* 2017, 8 (18), 3774.
349. Chen, Z.; Yang, D., et al., Final-2 targeted glycolysis mediated apoptosis and autophagy in human lung adenocarcinoma cells but failed to inhibit xenograft in nude mice. *Food and Chemical Toxicology* 2019, 130, 1-11.
350. Xia, S.; Duan, W., et al., GRP78 in lung cancer. *Journal of Translational Medicine* 2021, 19 (1), 1-14.
351. Bello-Perez, M.; Sola, I., et al., Canonical and noncanonical autophagy as potential targets for COVID-19. *Cells* 2020, 9 (7), 1619.
352. Wang, M.; Wey, S., et al., Role of the unfolded protein response regulator GRP78/BiP in development, cancer, and neurological disorders. *Antioxidants & redox signaling* 2009, 11 (9), 2307-2316.
353. Kania, E.; Pająk, B., et al., Calcium homeostasis and ER stress in control of autophagy in cancer cells. *BioMed research international* 2015, 2015.
354. Ma, X.; Guo, W., et al., Serum GRP78 as a tumor marker and its prognostic significance in non-small cell lung cancers: a retrospective study. *Disease markers* 2015, 2015.
355. Wu, J.; Wu, Y., et al., Targeted inhibition of GRP78 by HA15 promotes apoptosis of lung cancer cells accompanied by ER stress and autophagy. *Biology open* 2020, 9 (11), bio053298.
356. Parker, A. L.; Kavallaris, M., et al., Microtubules and their role in cellular stress in cancer. *Frontiers in oncology* 2014, 4, 153.
357. Parker, A. L.; Turner, N., et al., β III-Tubulin alters glucose metabolism and stress response signaling to promote cell survival and proliferation in glucose-starved non-small cell lung cancer cells. *Carcinogenesis* 2016, 37 (8), 787-798.
358. Rim, H.-K.; Cho, S., et al., T-type Ca²⁺ channel blocker, KYS05090 induces autophagy and apoptosis in A549 cells through inhibiting glucose uptake. *Molecules* 2014, 19 (7), 9864-9875.
359. Bootman, M. D.; Chehab, T., et al., The regulation of autophagy by calcium signals: do we have a consensus? *Cell Calcium* 2018, 70, 32-46.
360. Sallán, M. C.; Visa, A., et al., T-type Ca²⁺ Channels: T for Targetable. *Cancer research* 2018, 78 (3), 603-609.
361. Villar, V. H.; Durán, R. V., Glutamoptosis: a new cell death mechanism inhibited by autophagy during nutritional imbalance. *Autophagy* 2017, 13 (6), 1078-1079.
362. Bruntz, R. C.; Belshoff, A. C., et al., Inhibition of anaplerotic glutaminolysis underlies selenite toxicity in human lung cancer. *Proteomics* 2019, 19 (21-22), 1800486.
363. Pérez-Escuredo, J.; Dadhich, R. K., et al., Lactate promotes glutamine uptake and metabolism in oxidative cancer cells. *Cell cycle* 2016, 15 (1), 72-83.

364. Jin, L.; Alesi, G., et al., Glutaminolysis as a target for cancer therapy. *Oncogene* 2016, 35 (28), 3619-3625.
365. Sonveaux, P.; Végran, F., et al., Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. *The Journal of clinical investigation* 2008, 118 (12), 3930-3942.
366. Xie, W.-Y.; Zhou, X.-D., et al., Acid-induced autophagy protects human lung cancer cells from apoptosis by activating ER stress. *Experimental cell research* 2015, 339 (2), 270-279.
367. Lim, S.-C.; Kim, S. M., et al., Sodium salicylate switches glucose depletion-induced necrosis to autophagy and inhibits high mobility group box protein 1 release in A549 lung adenocarcinoma cells. *Oncology reports* 2008, 19 (5), 1165-1171.
368. Jiang, M.-j.; Dai, J.-j., et al., Aspirin in pancreatic cancer: chemopreventive effects and therapeutic potentials. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer* 2016, 1866 (2), 163-176.
369. Din, F. V.; Valanciute, A., et al., Aspirin inhibits mTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells. *Gastroenterology* 2012, 142 (7), 1504-1515. e3.
370. Perera, R.; Son, J., et al., Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. 2013.
371. Zhou, X.; Curbo, S., et al., Inhibition of glutamate oxaloacetate transaminase 1 in cancer cell lines results in altered metabolism with increased dependency of glucose. *BMC cancer* 2018, 18 (1), 1-14.
372. Kang, Y.-T.; Hsu, W.-C., et al., Metformin alleviates nickel-induced autophagy and apoptosis via inhibition of hexokinase-2, activating lipocalin-2, in human bronchial epithelial cells. *Oncotarget* 2017, 8 (62), 105536.
373. Chaudhri, V. K.; Salzler, G. G., et al., Metabolic alterations in lung cancer-associated fibroblasts correlated with increased glycolytic metabolism of the tumor. *Molecular Cancer Research* 2013, 11 (6), 579-592.
374. Wang, H.; Wang, L., et al., Inhibition of glycolytic enzyme hexokinase II (HK2) suppresses lung tumor growth. *Cancer cell international* 2016, 16 (1), 1-11.
375. Xi, F.; Ye, J., Inhibition of lung carcinoma A549 cell growth by knockdown of hexokinase 2 in situ and in vivo. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics* 2016, 23 (1-2), 53-59.
376. Wei, J.; Ma, Z., et al., miR-143 inhibits cell proliferation by targeting autophagy-related 2B in non-small cell lung cancer H1299 cells. *Molecular medicine reports* 2015, 11 (1), 571-576.
377. Lypova, N.; Telang, S., et al., Increased 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase-3 activity in response to EGFR signaling contributes to non-small cell lung cancer cell survival. *Journal of Biological Chemistry* 2019, 294 (27), 10530-10543.
378. Wang, Q.; Zeng, F., et al., Etk interaction with PFKFB4 modulates chemoresistance of small-cell lung cancer by regulating autophagy. *Clinical Cancer Research* 2018, 24 (4), 950-962.
379. Meng, M.-B.; Wang, H.-H., et al., Targeting pyruvate kinase M2 contributes to radiosensitivity of non-small cell lung cancer cells in vitro and in vivo. *Cancer letters* 2015, 356 (2), 985-993.
380. Zou, Y.-m.; Hu, G.-y., et al., Hypoxia-induced autophagy contributes to radioresistance via c-Jun-mediated Beclin1 expression in lung cancer cells. *Journal of Huazhong University of Science and Technology [Medical Sciences]* 2014, 34 (5), 761-767.
381. Hsu, H.-L.; Liao, P.-L., et al., Chloramphenicol induces autophagy and inhibits the hypoxia inducible factor-1 alpha pathway in non-small cell lung cancer cells. *International journal of molecular sciences* 2019, 20 (1), 157.
382. Nielsen, S. F.; Nordestgaard, B. G., et al., Statin use and reduced cancer-related mortality. *N Engl J Med* 2012, 367 (19), 1792-802.
383. Yang, Z.; Su, Z., et al., Fluvastatin Prevents Lung Adenocarcinoma Bone Metastasis by Triggering Autophagy. *EBioMedicine* 2017, 19, 49-59.
384. Sanli, T.; Liu, C., et al., Lovastatin sensitizes lung cancer cells to ionizing radiation: modulation of molecular pathways of radioresistance and tumor suppression. *J Thorac Oncol* 2011, 6 (3), 439-50.
385. Zhu, L.; Wang, Z., et al., Sphingosine kinase 1 enhances the invasion and migration of non-small cell lung cancer cells via the AKT pathway. *Oncol Rep* 2015, 33 (3), 1257-1263.
386. Gachechiladze, M.; Tichý, T., et al., Sphingosine kinase-1 predicts overall survival outcomes in non-small cell lung cancer patients treated with carboplatin and navelbine. *Oncol Lett* 2019, 18 (2), 1259-1266.
387. Song, L.; Xiong, H., et al., Sphingosine kinase-1 enhances resistance to apoptosis through activation of PI3K/Akt/NF- κ B pathway in human non-small cell lung cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2011, 17 (7), 1839-49.
388. Nagahashi, M.; Ramachandran, S., et al., Sphingosine-1-phosphate produced by sphingosine kinase 1 promotes breast cancer progression by stimulating angiogenesis and lymphangiogenesis. *Cancer research* 2012, 72 (3), 726-735.
389. Dall'Armi, C.; Devereaux, K. A., et al., The role of lipids in the control of autophagy. *Current biology : CB* 2013, 23 (1), R33-45.
390. Cho, J. H.; Hong, S. K., et al., Overexpression of phospholipase D suppresses taxotere-induced cell death in stomach cancer cells. *Biochimica et biophysica acta* 2008, 1783 (5), 912-23.
391. Hsu, Y. L.; Hung, J. Y., et al., Phospholipase D signaling pathway is involved in lung cancer-derived IL-8 increased osteoclastogenesis. *Carcinogenesis* 2010, 31 (4), 587-96.

392. Ahn, M.-J.; Park, S.-Y., et al., A Single Nucleotide Polymorphism in the Phospholipase D1 Gene is Associated with Risk of Non-Small Cell Lung Cancer. *Int J Biomed Sci* 2012, 8 (2), 121-128.
393. Shatz, O.; Holland, P., et al., Complex Relations Between Phospholipids, Autophagy, and Neutral Lipids. *Trends in biochemical sciences* 2016, 41 (11), 907-923.
394. Meacci, E.; Vasta, V., et al., Effect of Rho and ADP-ribosylation Factor GTPases on Phospholipase D Activity in Intact Human Adenocarcinoma A549 Cells*. *Journal of Biological Chemistry* 1999, 274 (26), 18605-18612.
395. Meacci, E.; Nuti, F., et al., Activation of Phospholipase D by Bradykinin and Sphingosine 1-Phosphate in A549 Human Lung Adenocarcinoma Cells via Different GTP-Binding Proteins and Protein Kinase C Delta Signaling Pathways. *Biochemistry* 2003, 42 (2), 284-292.
396. Granade, M. E.; Harris, T. E., Purification of Lipin and Measurement of Phosphatidic Acid Phosphatase Activity from Liposomes. *Methods Enzymol* 2018, 607, 373-388.
397. Fan, X.; Weng, Y., et al., Lipin-1 determines lung cancer cell survival and chemotherapy sensitivity by regulation of endoplasmic reticulum homeostasis and autophagy. *Cancer medicine* 2018, 7 (6), 2541-2554.
398. Nazim, U. M.; Moon, J.-H., et al., PPAR γ activation by troglitazone enhances human lung cancer cells to TRAIL-induced apoptosis via autophagy flux. *Oncotarget* 2017, 8 (16), 26819-26831.
399. To, K. K. W.; Wu, W. K. K., et al., PPAR γ agonists sensitize PTEN-deficient resistant lung cancer cells to EGFR tyrosine kinase inhibitors by inducing autophagy. *Eur J Pharmacol* 2018, 823, 19-26.
400. Gkoutakos, A.; Sartori, G., et al., PTEN in Lung Cancer: Dealing with the Problem, Building on New Knowledge and Turning the Game Around. *Cancers* 2019, 11 (8), 1141.
401. Li, M. Y.; Yuan, H., et al., Roles of peroxisome proliferator-activated receptor- α and - γ in the development of non-small cell lung cancer. *American journal of respiratory cell and molecular biology* 2010, 43 (6), 674-83.
402. Freitas, R. D. S.; Campos, M. M., Protective Effects of Omega-3 Fatty Acids in Cancer-Related Complications. *Nutrients* 2019, 11 (5), 945.
403. Yang, P.; Cartwright, C., et al., Anticancer activity of fish oils against human lung cancer is associated with changes in formation of PGE2 and PGE3 and alteration of Akt phosphorylation. *Mol Carcinog* 2014, 53 (7), 566-577.
404. Zajdel, A.; Wilczok, A., et al., Toxic effects of n-3 polyunsaturated fatty acids in human lung A549 cells. *Toxicology in vitro : an international journal published in association with BIBRA* 2015, 30 (1 Pt B), 486-91.
405. Yao, Q. H.; Zhang, X. C., et al., ω -3 polyunsaturated fatty acids inhibit the proliferation of the lung adenocarcinoma cell line A549 in vitro. *Mol Med Rep* 2014, 9 (2), 401-6.

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