Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2023**; 28(3): 47
https://doi.org/10.31083/j.fbl2803047

Review

Potential Therapeutic Targets in Ovarian Cancer: Autophagy and Metabolism

Misung Park[1,2,†], Soohyun Choe[1,†], Miyoung Shin[3,†], Ayoung Kim[1], Kyumin Mo[1], Hyeonseok Kwon[1], Hyunho Yoon[1,2,*]

[1]Department of Medical and Biological Sciences, The Catholic University of Korea, 14662 Bucheon, Republic of Korea
[2]Department of Biotechnology, The Catholic University of Korea, 14662 Bucheon, Republic of Korea
[3]Department of Pathology, Yale University School of Medicine, New Haven, CT 06510, USA
*Correspondence: hyoon@catholic.ac.kr (Hyunho Yoon)
[†]These authors contributed equally.

Academic Editors: Kavindra Kumar Kesari and Dhruv Kumar
Submitted: 30 January 2023 Revised: 18 February 2023 Accepted: 1 March 2023 Published: 10 March 2023

Abstract

Ovarian cancer (OC) is characterized by high mortality rates owing to late diagnosis and resistance to chemotherapy. Autophagy and metabolism play essential roles in the pathological process of cancer and have recently been proposed as potential targets for anticancer therapies. Autophagy is responsible for the catabolic clearance of functionally misfolded proteins and plays different roles depending on the stage and type of cancer. Thus, understanding and controlling autophagy is relevant for treating cancer. Autophagy intermediates can communicate with each other by providing substrates for glucose, amino acid, and lipid metabolism. Metabolites and metabolic regulatory genes modulate autophagy and influence the immune response. Therefore, autophagy and the functional manipulation of metabolism during starvation or overnutrition are being investigated as potential therapeutic targets. This review discusses the role of autophagy and metabolism in OC and highlights effective therapeutic strategies targeting these processes.

Keywords: ovarian cancer; autophagy; metabolism; metabolites; cancer therapeutics

1. Introduction

Ovarian cancer (OC) is a malignant tumor that develops in the ovary and is the most lethal among female genital cancers [1]. Most cases are closely related to heredity, which is mainly caused by mutations in genes such as *BRCA1*, *BRCA2*, *BRIP1*, *RAD51C*, and *RAD51D*. Epithelial ovarian cancer (EOC) is a type of cancer that arises from the tissue covering the ovary. EOC is the most common cause of gynecological cancer-related death and usually occurs in postmenopausal women [2]. *BRCA1/2* germline mutations are the strongest known genetic risk factors for this type of cancer. In fact, these mutations are found in 6–15% of women with epithelial ovarian cancer. Knowing a patient's *BRCA1/2* status can be useful for counseling regarding expected survival. Studies have shown that BRCA1/2 carriers respond better than non-carriers to platinum-based chemotherapies, which are commonly used to treat ovarian cancer. As a result, carriers of BRCA1/2 mutations have a greater chance of survival, even though the disease is generally diagnosed at a later stage and higher grade [3]. Depending on their origin, ovarian cancers are classified into three types: epithelial, germ cell, and sex cord-stromal cancers [2]. Ovarian carcinosarcoma is known as malignant mixed Müller tumor. Ovarian carcinosarcoma is rare, biphasic consisting of epithelial and sarcoma components, accounting for only 1–4% of all ovarian cancers. Their prognosis is dismal, and most patients relapse within 1 year of completing initial treatment [4]. OC is difficult to treat due to ineffective screening strategies and delayed diagnosis [5]. CA-125, a serum molecule, is commonly used as an OC diagnostic biomarker [6]. Currently, promising biomarkers discovered by proteomic analysis include transferrin and apamin, which are potential secondary markers for CA-125 [7]. Recent proteomics analyses provide new treatment options that may reduce resistance to drug treatment in ovarian cancer, potentially improving patient outcomes [8]. However, these biomarkers still have limited sensitivity and specificity, which are insufficient for early OC detection [9]. Therefore, no single test or method is currently capable of the early diagnosis of OC.

OC can be highly dispersed after it arises from the primary site. OC metastasis is controlled by various cellular pathways and factors in the tumor microenvironment (TME) [10]. Tumor cells must change shape to migrate from where they originated, which explains why tumors that undergo epithelial-mesenchymal transition (EMT) can easily become more malignant [11]. A comprehensive understanding of the pathways involved in cancer development may be a key to cancer treatment. In particular, in EMT, various signaling pathways, such as transforming growth factor-β (TGF-β), Notch, Wnt/β-catenin, and PI3K-AKT-mTOR act as regulators [12,13]. Dysregulation of these signaling pathways is critical for cell survival, growth, and proliferation in tumorigenesis, providing clinically useful targets for effectively enhancing OC survival [14–17].

Autophagy is an intracellular degradation system that eliminates damaged organelles and misfolded proteins to maintain cell's biological functions and homeostasis [18]. Autophagy removes damaged material and recycles it to create new building blocks or convert it into an energy source [19]. To date, three types of autophagy have been studied: macroautophagy, microautophagy, and chaperone-mediated autophagy. As macroautophagy has been the most widely studied, the term "autophagy" usually refers to macroautophagy. The autophagy system has a central lysosome containing more than 60 luminal hydrolases involved in the PI3K-AKT-mTOR, Ras-Raf-MAPK, TP53, and Beclin1 pathways, which play essential roles in cancer progression and metastasis [20,21]. These findings suggest that cancer may be associated with autophagy dysregulation [21,22]. Therefore, autophagy-mediated pathways may be potential targets for cancer-targeted therapies.

Cancer cell metabolism plays a crucial role in cancer progression and survival. As the persistent uncontrolled proliferative signal is one of the common cancer features, metabolic processes can promote cancer cell proliferation and motility [23]. Metabolic processes and their metabolites provide energy for uncontrolled growth through necessary nutrients and components that can modulate the expression of specific genes and proteins involved in tumorigenesis [24]. This review discusses the importance of autophagy and metabolism, including glucose, amino acid, and lipid metabolism in OC and the clinical potential of targeting these cellular processes in OC therapy.

2. Autophagy in Cancer

Autophagy plays various physiological roles and consists of several steps. Autophagy begins in preautophagosomal structures and templates the size and shape of the phgophore according to its cargo [25]. One of the major degradation mechanisms of autophagy is mediated by unique organelles called autophagosomes, which are double-membrane vesicles containing cytoplasmic components [26]. Autophagosomes can derive membranes from multiple sources, including the endoplasmic reticulum, Golgi apparatus, and plasma membranes [27]. Autophagy-related protein 8 (ATG8) on the surface of the autophagosome is removed by ATG4 and Ymr1, leading to autophagosome maturation [28]. After maturation, vesicles fuse with lysosomes or endosomes to form autophagolysosomes, and the cytoplasmic material is degraded by the catalytic activation of lysosomal hydrolases [29]. The fusion of autophagosomes and lysosomes is affected by soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) proteins, Rab family proteins, phosphoinositide 3-kinase (PI3K) complex, and Rubicon [30]. In particular, Rubicon is related to an increase in nonalcoholic fatty liver disease (NAFLD) by influencing the autophagosome-lysosome fusion stage [31].

As excessive self-consumption can be detrimental to the cell, autophagy is controlled by a series of proteins known as Unc-51-like kinase 1 (ULK1) and 2 (ULK2), which form complexes with ATG13, ATG101, and focal adhesion kinase (FAK) family kinase-interacting protein of 200 kDa (FIP200), which plays critical roles in autophagy initiation [32]. Autophagy is mainly regulated by the AMPK and mTORC1 patways. Autophagy is activated by AMPK when cells are in nutrient deprivation or oxidative stress. In contrast, mTORC1 inhibits autophagy by reducing UKL1 activation under nutrient-rich conditions [33,34]. As such, autophagy is regulated to maintain normal cell homeostasis (Fig. 1).

In cancer, autophagic processes are closely related to apoptosis and cell survival and can act as a double-edged sword [35,36]. Several studies have revealed that the role of autophagy differs according to the stage of tumor development. Autophagy is a tumor suppressor in the early stages of tumorigenesis and can promote tumor progression in advanced stages [35]. Autophagy is mainly inhibited by the PI3K-AKT-mTOR axis, promoting the expression of various tumor suppressors, such as LKB1, TSC, and p53 [37,38]. Beclin1 is deleted in several tumor types and is a tumor suppressor in mice [39]. In addition, depletion of the *BECN1* gene encoding Beclin1 restricts tumor cell growth and metastasis in several cancers, including ovarian and breast cancers [40]. Conversely, tumor cells may be more dependent on autophagy for their survival. Autophagy plays an important role in tumor progression and is essential for tumor cell survival by RAS activation [41,42]. Autophagy also promotes EMT and metastasis under starvation conditions [43,44]. These studies indicate that effective regulation of autophagy in cancer can be a promising strategy for cancer treatment.

3. Metabolism in Cancer

3.1 Glucose Metabolism

Glucose synthesizes adenosine triphosphate (ATP), an essential energy source for most cells, including cancer cells. The absorbed glucose is converted into pyruvate by glycolysis. Under normoxic conditions, pyruvate enters the mitochondria and generates approximately 38 ATP molecules via the tricarboxylic acid (TCA) cycle. However, when oxygen is insufficient, pyruvic acid is converted to lactic acid, and only 2 ATP molecules are produced through anaerobic glycolysis. A completely different phenomenon occurs in tumors, called the Warburg effect (Fig. 2). Tumor cells use a less efficient process of 'aerobic glycolysis' despite having sufficient oxygen, to gain energy faster [45]. As markedly increasing glucose is a prominent feature of cancer, targeted cancer therapy is possible using the glucose analog radiotracer 18 fluoro-2-deoxy-D-glucose (FDG) [45].

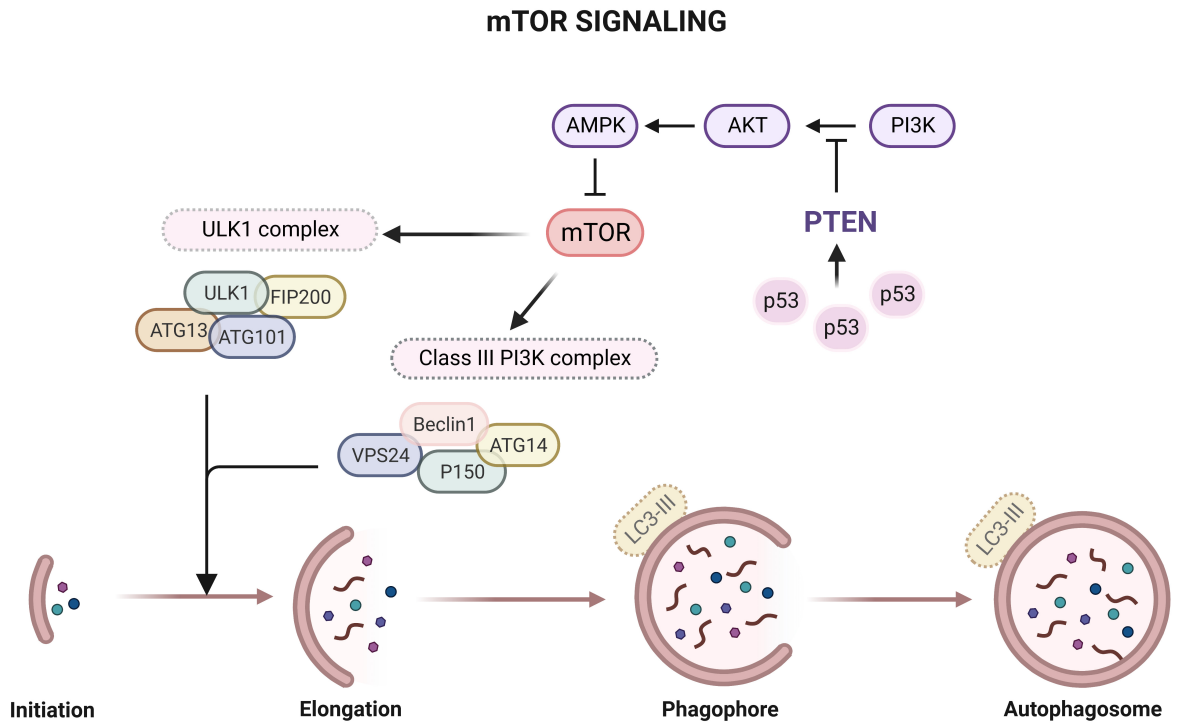

Fig. 1. Signaling pathways regulating autophagy. mTOR signaling is involved in the autophagy process, which is controlled by PTEN that is regulated by p53. Inactivated mTOR enhances autophagosome initiation through the ULK1 complex and the class III PI3K complex. In cancer cells, LC3-II is a protein attached to the autophagosome and is a marker of autophagy activity. mTOR-mediated complexes can be potential clinical targets. AMPK, AMP-activating protein kinase; FIP, FAK family kinase-interacting protein of 200 kDa; PTEN, Phosphatase and Tension Homolog; ULK1, Unc-51-like kinase 1; VPS24, Vacuolar protein sorting 24.

3.2 Amino Acid Metabolism

Amino acids are basic nutrients required to produce proteins necessary for tumor progression. Amino acids can be classified as essential and non-essential, both involved in cancer development. Cancer cells can settle the structure by the biosynthesis of proteins and nucleic acids, participate in redox reactions to alleviate oxidative stress and contribute to immune evasion [46,47]. Unlike non-essential amino acids (NEAA) that are acquired through most cellular systems, essential amino acids are acquired by dietary intake. Branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine, can not only promote protein synthesis and oxidation, but also interact with the mTOR pathway during tumor growth, eventually leading to nucleotide synthesis [48,49]. In particular, leucine, the most abundant amino acid, can trigger mTORC1 signaling by activating the sensor protein Sestrin2 [49,50]. In addition, Sestrin2 inhibits mTORC1, which is strongly associated with cell growth and is regulated by protein/lipid synthesis and autophagy [49,51,52]. BCAAs can be beneficial in providing nitrogen and carbon groups, supplement energy, epigenetic modulation, and lipogenesis [46,53]. In addition, BCAA metabolism can be a carbon frame for fatty acids and control fatty acid oxidation (FAO) [54]. Thus, upregulated BCAA can induce tumor growth, implying that BCAA-mediated metabolism may be an important target for cancer therapy.

Glutamine is an amino acid required for the proliferation of cancer cells because it contributes to the biosynthesis of various proteins, lipids, and nucleic acids by supplying carbon and nitrogen [46,55]. Glutamine serves amide nitrogen of asparagine and can be converted to glutamate [53]. Some NEAAs like alanine, aspartate, and phosphoserine can be produced from glutamate [53]. Glutamine requirements in cancer cells are increased primarily through amino acid transporters such as alanine/serine/cysteine (ASC) [46]. Some types of cancer experience ‘glutamine addiction’, requiring glutamine for survival and relying on glutamine supplementation and new TCA cycles [46,56]. Glutamine can also function in mTORC1pathway by promoting the outflow of essential amino acids and glutamine catabolism, thus inhibiting autophagy [57].

3.3 Lipid Metabolism

Lipids are efficient energy sources composed of fatty acids (FAs), triacylglycerols (TGs), waxes, phospholipids, sphingolipids, and isoprenoids. FAs are the major form of energy storage and are composed of TGs and glycerol [58]. FAO provides more usable energy, such as high-energy phosphates. Additionally, the degradation of lipids stored in lipid droplets (LDs) can be utilized through lipolysis and autophagy [59]. In cancer cells, lipid metabolism is regulated for membrane construction and energy storage,

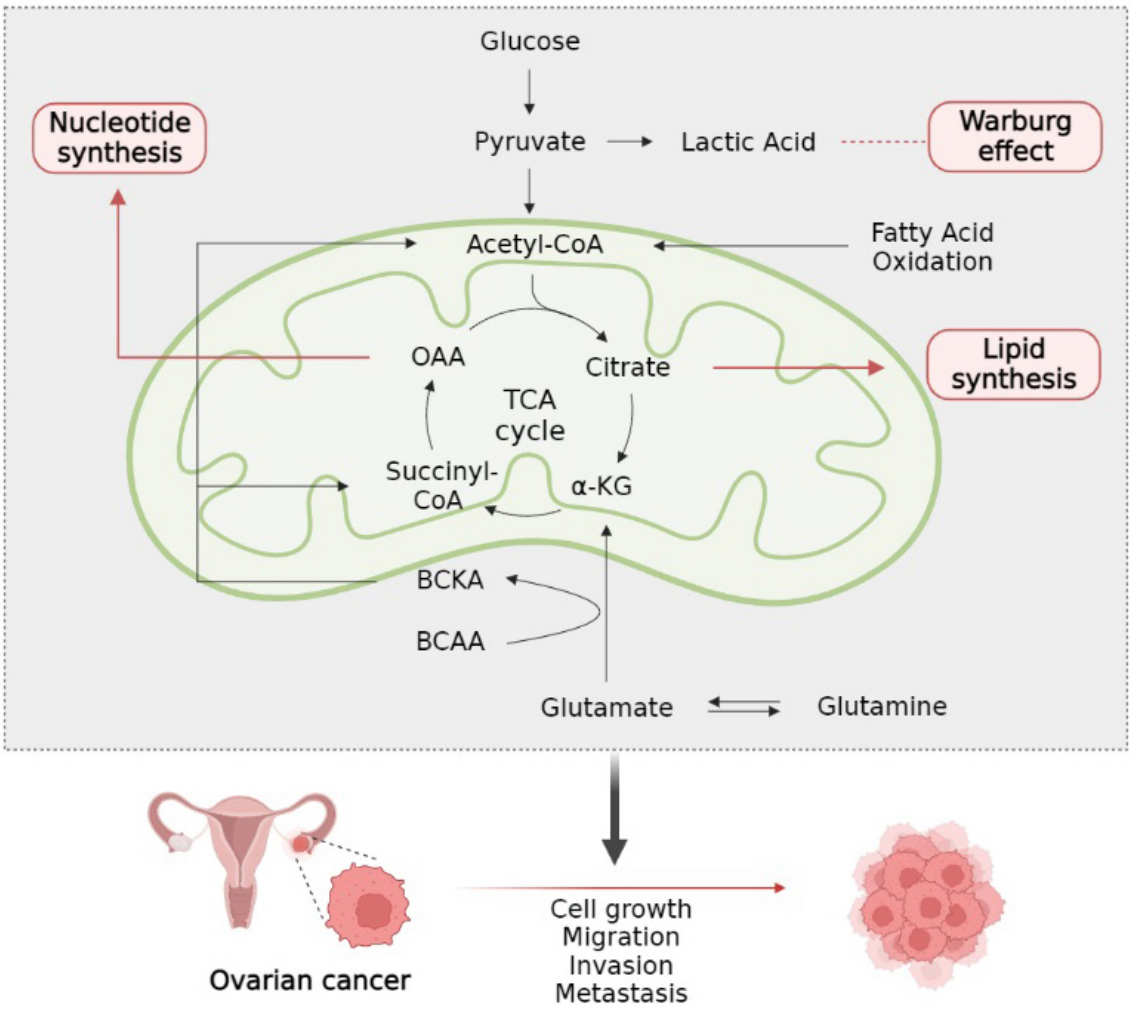

Fig. 2. Crosstalk between OC cells and metabolic reprogramming. Most cancer cells, including OC, increase glucose uptake and lactate production, which is called the Warburg effect. Aerobic glycolysis, glutamine catabolism, and lipid and nucleotide synthesis, support cell growth, migration, invasion, and metastasis in OC, which are potential clinical targets in OC treatment.

making second messengers for signaling pathways and providing ATP with FAO when more energy is required [60]. Therefore, *de novo* synthesis of FAs can be activated for tumor growth even under harsh conditions. Lipogenesis-related enzymes such as ATP citrate lyase, acetyl-CoA carboxylase, and fatty acid synthase are commonly overexpressed in tumors and can promote cell proliferation and survival [59,61]. FAO can also modulate metabolic oxidative stress dealing with reactive oxygen species (ROS) in tumors [62]. Monoacylglycerol lipase converts monoacylglycerol to free fatty acids and glycerol during tumorigenesis, which may enhance the population of highly advanced cancer cells *via* the EMT [60,61].

4. Autophagy in OC

Dysregulation of autophagy in OC is caused by factors [63], such as mutation of *LC3* and *Beclin1*; tumor suppressors PTEN and p53; and growth factor pathways, PI3K-AKT-mTOR. LC3 are often lowly expressed in malignant cells, preventing the accumulation of LC3-marked autophagosomes in aggressive OC [64]. In addition, deletion of *Beclin1*, a tumor suppressor gene, was found in more than 50% of OCs [65], suggesting that the upregulation of *LC3* and *Beclin1* can be an effective treatment for OC. Overexpression of p53 inhibits autophagy, and the PI3K-AKT-mTOR axis upregulation activates autophagy by inactivating PTEN in OC cells [66,67]. These results demonstrate that p53 and PTEN can be important regulators of autophagy in OC.

The TME affects tumor cell growth, metastasis, and immunity [68]. Direct or cytokine-mediated interactions between cancer cells and TME components promote tumor growth and metastasis [69–71]. The TME response to stressors, such as hypoxia and inflammation, responses tumor initiation and development. The interaction between the TME and autophagy in tumor cells can promote tumor development by protecting cells from stressors.

Various inflammatory factors in TME can induce autophagy. In TME, the cytokine IL-6 secreted by cancer-associated fibroblasts (CAFs) accumulates in the ascites of OC [72]. IL-6, which is associated with the invasiveness and metastasis of OC cells, induces autophagy by phosphorylating the signal transducer and the activator of transcription 3 (STAT3), inducing the expression of NS5ATP9 [73,74]. In addition, lysophosphatidic acid (LPA), abundantly secreted from the TME of OC, increases the aggressiveness of OC and inhibits autophagy [75,76], suggesting that even cytokines that induce aggressiveness in OCs may act differently in regulating autophagy.

5. Crosstalk between Autophagy and Metabolism in OC

Autophagy and metabolism commonly supply energy and nutrients to cells. Autophagy is strongly associated with cancer cell metabolism by maintaining cell metabolic processes [77]. For example, tumor cells increase glycolysis to obtain the necessary metabolic intermediates through mitochondrial metabolism [78]. To maintain mitochondrial metabolism, autophagy degrades membrane organelles to provide substrates, such as glycogen, amino acids, and lipids, suggesting that autophagy-mediated metabolites alter cancer cell function in OC (Fig. 3). In addition, autophagy itself is regulated by metabolic hormones and participates in cellular homeostasis by recycling metabolites [79].

5.1 Interaction between Autophagy and Glucose Metabolism in OC

Glucose metabolism plays an essential role in autophagy-regulated glycolysis in cancer cells. As mentioned above, glucose deprivation stimulates autophagy through AMPK activation and mTORC1 inactivation. In contrast, excess nutrients inhibit autophagy [80]. Conversely, activation of glucagon in the liver activates cyclic adenosine monophosphate (cAMP) production, which stimulates autophagy [81]. AMPK, induced under starvation, can stimulate the phosphorylation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) to promote glycolysis [82]. GAPDH forms a complex with Rheb, and hexokinase-II (HK-II) inhibits mTOR by binding to mTORC1 [83]. These results imply that autophagy can be induced by HK-II-mediated mTOR inactivation. However, inhibition of HK-II promotes apoptosis under glucose-starvation conditions [83]. LPA, which is abundant in ascites, stimulates aerobic glycolysis in OC [84] and increases hypoxia-inducible factor 1-alpha (HIF1α) levels *via* Rac1-NOX-ROS signaling, upregulating the expression of HK-II and consequently leading to a glycolytic shift in OC cells [85]. Treatment with 3-bromopyruvate, an inhibitor of HK-II, significantly reduced tumor burden in an OC mouse model [84,86], suggesting that aerobic glycolysis regulated by HK-II may be a therapeutic target for OC.

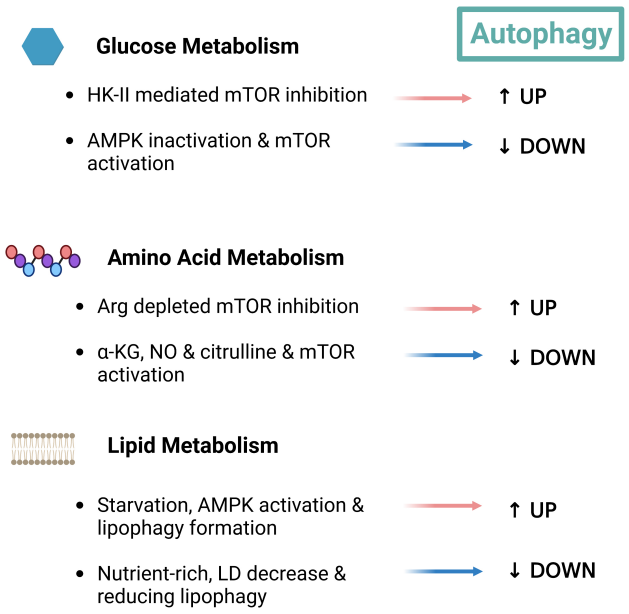

Fig. 3. Autophagy-mediated metabolism in OC. Autophagy and metabolic processes interact through the regulation of several proteins and signals. Under glucose deprivation, HK-II-mediated inhibition enhances the autophagy process by enhancing LPA and HIF1α. Free fatty acid-mediated AMPK activation also increases lipophagy. mTOR activation with α-KG reduces autophagy by regulating proteins, such as NO and citrulline. In lipid metabolism, lipophagy is reduced by the lipolysis of lipid droplets. HK-II, hexokinase-II; LPA, lysophosphatidic acid; HIF1α, hypoxia-inducible factor 1-alpha; AMPK, AMP-activating protein kinase; NO, nitric oxide; LD, lipid droplet; Arg, Arginine; α-KG, alpha-ketoglutarate.

5.2 Interaction between Autophagy and Amino Acid Metabolism in OC

Amino acids are essential for the synthesis of proteins, nucleic acids, and lipids, which are important for cancer growth [87]. Amino acids and their metabolites play key roles in regulating mTORC1 and inhibiting autophagy [88]. In general, extracellular glutamine is critical for the survival of many tumor cells [89]. Interestingly, low-invasive OC cells are glutamine-independent for glucose metabolism, whereas highly invasive OC cells are glutamine-dependent [89]. Glutamine, metabolized by glutaminase (GLS), produces glutamate and ammonia. Glutamate is oxidatively deaminated by glutamate dehydrogenase (GLUD1) and converted to α-ketoglutarate (α-KG), a TCA cycle-replenishing substrate [90,91]. In highly invasive OC cells, inhibition of the TCA cycle by glutamine reduces tumor cell invasiveness, whereas adding α-KG restores the invasive ability of OC cells [89]. Since α-KG is known to inhibit autophagy, whereas ammonia has been reported to induce autophagy [92,93]. Thus, balance between ammonia and α-KG is important for the regulation of autophagy in OC.

Cancer cells also use arginine to grow and migrate [94]. Arginine depletion by arginine deiminase (ADI) inhibited the mTORC1 pathway to induce autophagy in many cancer cell types [95]. The arginine metabolites, nitric oxide (NO) and citrulline, can also inhibit autophagy by activating mTORC1 [96]. Arginine deficiency induces autophagy and poor viability in OC cells, suggesting that autophagy is important for tumor survival under stress [97,98]. Rag GTPases are heterodimeric complexes composed of activated forms of Rag A/B and inactivated forms of Rag C/D, enhancing mTORC1 activation [99,100]. Activation of Rag A/B requires CASTOR1, a homodimer or heterodimer of CASTOR1 and CASTOR2. Arginine can directly bind only to CASTOR1. Consequently, the CASTOR1–CASTOR2 complex is disrupted, leading to mTORC1 activation [101,102]. Given that arginine can be an amino acid sensor to inhibit autophagy [103], joint targeting of autophagy and metabolic processes in mTORC1-activated cells can be a promising anti-OC strategy.

5.3 Interaction between Autophagy and Lipid Metabolism in OC

Lipid metabolism and autophagy interact during cancer progression. Lipophagy, an autophagy process, is a conserved secondary mechanism of lipid breakdown and alternative energy sources when nutrients are scarce [104,105]. Lipids degraded by lipophagy are stored in LDs to provide the necessary energy to growing tumors [59]. During starvation, stored lipids are broken down to release free fatty acids, which are an efficient source of energy [59]. Acetyl coenzyme A (Acetyl-CoA), nicotinamide adenine dinucleotide (NADH), and flavin adenine dinucleotide hydroquinone (FADH2) produced by FAO can generate ATP to provide energy in a hypoxic tumor environment [59]. Increased FAO ratios in OC contribute to cisplatin resistance. Cisplatin, a platinum-based drug, is widely used for OC chemotherapy [106,107]. These results suggest that supplemental and increased lipid storage of LDs is beneficial for proliferation and resistance in OC.

Lipophagy can be a double-edged sword that plays a role in cancer progression or inhibition. Lipid catabolism can be regulated by transcription factors, such as lysosomal acid lipase (LAL), or forkhead homeobox protein O1 (FOXO1) [108,109], which control immature myeloid-derived suppressor cells (MDSCs). Increased MDSCs were known to regulating the immune response and promote tumor cell angiogenesis, invasion, and metastasis [110]. In contrast, LAL acts as a tumor suppressor to reduce the metastasis of lung and liver cancers [111]. Therefore, a comprehensive understanding of autophagy and lipid metabolism is essential, which may lead to new anticancer therapies for OC patients.

6. Crosstalk between Autophagy/Metabolism and Immune Cells in OC

Autophagy and metabolic processes in cancer cells are strongly associated with the immune system. Avoiding the immune destruction of cancer cells is a novel feature of cancer. Immune cells in the TME play an important role in OC [23]. EOC, an immunogenic tumor, is strongly associated with tumor-infiltrating lymphocytes (TILs) [112]. Several studies have shown the association between TIL and survival in OC, where patients with TIL were more likely to have a favorable outcome [113,114]. However, response rates are only 10–15%, with drug resistance developing in early clinical trials, and no immune checkpoint inhibitors are currently approved by the FDA [115]. Since PD-L1 expression is rare in EOC, it is necessary to further investigate potential predictive biomarkers for immune checkpoint inhibitors and elucidate the key mechanisms regulating immune suppression in EOC. Phosphatase and tensin homolog (PTEN) is a protein and lipid phosphatase known to act as a tumor suppressor and an autophagy regulator gene [72,116]. In OC, the inactivation of PTEN generally activates the PI3K-AKT signaling pathway, which inhibits T cell invasion [117]. In addition, PTEN can trigger the recruitment of immune cells such as natural killer (NK), dendritic (DCs), and T cells for antitumor immunity [118].

PTEN is also closely related to regulators of autophagy and metabolic processes. Inhibition of PI3K-AKT signaling by PTEN inhibits the mTOR pathway, which can regulate autophagy-sensing metabolic conditions [72,119]. Further studies using PTEN transgenic mice demonstrated that PTEN induced an “anti-Warburg effect”, which is highly related to glucose metabolism [116,120]. PTEN regulates the expression of glucose transporter 1 (GLUT1) in the plasma membrane by inhibiting AKT to reduce glucose uptake in OC [121]. These results suggest that various immune cells can be regulated by autophagy and metabolic processes via PTEN. Thus, loss of PTEN is relevant to the immune evasion of cancer cells including OC.

In addition, the interaction between programmed cell death-ligand-1 (PD-L1), mainly produced by macrophages, and programmed cell death-1 (PD-1) from lymphocytes is related to the immune processes in cancer [116,122]. PD-L1 and PD-1 are well-known immune checkpoint inhibitors. In particular, PD-L1 regulates glucose metabolism in sarcomas and affects autophagy by activating mTORC1 in OC [123]. In general, PD-L1 negatively regulates T-cell function and is expressed in most tumor cells in the TME. One of the distinctive features of PD-L1 is the suppression of immune responses, especially in OC, where increased PD-L1 promotes the AKT-mTOR pathway for cell proliferation and induces BECN1-induced autophagy [124]. In patients with invasive EOC, high PD-1 and PD-L1 expression leads to beneficial survival outcomes [114,122], suggesting that immune checkpoint inhibitors can modulate the proportion of immune cells in OC, which may include autophagy

Table 1. Inhibitors targeting autophagy and metabolism in OC.

Cellular target	Drug	Function	FDA-approval	Reference
Autophagy	Rapamycin	Inhibits PI3K-AKT-mTOR signaling pathway	Yes	[128]
	Bortezomib	Inactivates proteasome active sites	Yes	[125]
	Elaiophylin	Arrests autophagic flux by alleviating lysosomal cathepsin activity	No	[126]
	Danusertib	Suppresses aurora kinase to induce apoptosis	No	[127]
Metabolism	Daporinad	Inhibits NAMPT	No	[129]
	Triapine	Downregulates RNR and sensitizes OC to PARP inhibitors	No	[130]
	Pemetrexed	Antimetabolite that represses thymidylate synthase	Yes	[131]

NAMPT, nicotinamide phosphoribosyltransferase; RNR, ribonucleotide reductase; PARP, poly (ADP-ribose) polymerase.

and metabolic processes.

7. Autophagy and Metabolic Targeted Therapy in OC

Correlation of autophagy and metabolism is critical in anticancer therapy since autophagy is a major contributor in cellular metabolism regulating metabolic homeostasis [81]. Therapeutic strategies targeting autophagy and metabolism are still being evaluated in several clinical and preclinical trials for OC (Table 1, Ref. [125–131]). Rapamycin, a well-known autophagy activator, affects the translational initiation of OCs *via* the mTORC1 pathway and eukaryotic translation initiation factor 4E (elF4E) [132]. Although rapamycin efficiently inhibits the activity of mTORC1 serine/threonine kinase, its clinical use has not been successful because of its low water solubility. Therefore, other effective mTORC1 inhibitors are being screened for regulating autophagy [133]. Bortezomib also inhibits autophagy by reducing cathepsin levels in OC and is particularly effective when combined with cisplatin [125]. Cisplatin is a classic platinum-based chemotherapy for OC. The fundamental mechanism of cisplatin is to bind DNA in the nucleus to hinder its transcriptional or replicational functions, resulting in cell death [134]. Although cisplatin has therapeutic properties, it can function synergistically with other therapies. In addition, combinations of PARP inhibitors with conventional chemotherapeutic agents that induce DNA strand breaks are also being considered. Given that inhibition of PARP in normal cells abolishes important mechanisms of DNA repair in these cells, chemotherapy-induced myelosuppression is enhanced. As such, a major concern with this multimodal treatment approach is the high risk of overlapping myelotoxicity. Consequently, dose adjustment of both regimens is recommended [135].

Elaiophyllin, another autophagic inhibitor, induces cell death in OC [126]. Elaiophyllin also directly induced apoptosis *in vivo* and sensitized an animal OC model to cisplatin [127]. Danusertib is an inhibitor of the aurora, a kinase that is essential for cell proliferation. Danusertib induces cell cycle arrest and autophagy by inhibiting the PI3K-AKT-mTOR signaling pathway in OC cell lines [127]. Notably, it inhibits the PI3K-AKT-mTOR signaling pathway in OC cell lines, leading to induced cell cycle arrest and autophagy, which ultimately inhibits cancer metastasis by reducing EMT through the vimentin regulation [127].

Metabolic modulators, such as daporinad, triapine, and pemetrexed, have been evaluated in patients with OC. Daporinad (APO866, FK866) is a nicotinamide phosphoribosyltransferase (NAMPT) inhibitor that affects more resistant cells than sensitive cells upon deprivation of NAD+ metabolic synthesis [136]. Moreover, carboplatin and daporinad combined showed better results in inhibiting resistant cell proliferation in OC [136]. Although daporinad has a feasible anticancer ability, it has failed in phase I/II clinical trials [137]. Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone), a small-molecule inhibitor, inactivated ribonucleotide reductase (RNR) to downregulate nucleotide metabolism [138]. Interestingly, continuous treatment with cisplatin followed by triapine showed a synergistic effect, whereas concurrent treatment with triapine and cisplatin showed an inverse correlation [138]. Pemetrexed has antitumor activity in OC by modulating thymidylate synthesis in purine metabolism, which is being studied in a cancer phase III trial [139,140]. Given the propensity for OC in glutamine addicts and the association between glutamine and nucleotide metabolism, pemetrexed may be used to treat OC patients [141].

During glucose deprivation, HK-II facilitates the transition from glycolysis to autophagy by inhibiting mTORC1 binding. HK-II cooperates with extracellular signal-regulated kinase (ERK)-mediated autophagy to induce cisplatin-resistant OCs [142]. Thus, higher HK-II expression is strongly associated with progressive OC associated with tumor cell migration and invasion [143]. In particular, the glucose analog 2-deoxy-D-glucose (2-DG) can reverse autophagy in glucose deprivation by inhibiting HK-II glycolysis, while it inhibits glucose metabolism by reducing glucose uptake under calorie-restricted conditions [83,144]. However, 2-DG remains in phase I clinical trials because 2-DG dramatically reduced white blood cell counts and glycemic index in patients with glioma and leukemia undergoing radiation therapy [145].

Resveratrol (3,5,4'-trihydroxystilbene) may be another promising therapy for modulating glucose metabolism in OC [144]. In a mouse model, resveratrol

significantly reduced the cell growth of OCs [146]. In addition, resveratrol can induce a nutritionally deprived state through suppression of glucose uptake, lactate production, and reduction of AKT-mTOR signaling, eventually leading to starvation-induced autophagy [144]. The expression of ATG5 and ROS was positively correlated with resveratrol treatment, which could induce autophagy and apoptosis [147]. Resveratrol also affects IL-6-induced OC migration and inhibits cisplatin-induced EMT, demonstrating that resveratrol treatment can also be performed in advanced OC [147,148]. In addition, resveratrol can be used in combination with conventional therapeutic adjuvants, especially in chemoresistant OC cells. Resveratrol can alleviate EMT by regulating EMT transcription factors and this effect can be enhanced when combined with cisplatin [149]. These studies suggest that therapeutic strategies targeting autophagy and metabolism could be promising, and the clinical evaluation of these treatments is ongoing in OC.

8. Conclusions

Autophagy can be either a tumor-suppressing or tumor-promoting process, depending on the oxidative stress, nutrient deficiency, chemotherapy, and the stage of cancer. In addition, metabolic regulation involving glucose, amino acids, and lipids, which are essential nutrients for cell survival, is an important feature of cancer cells. Numerous studies have suggested that regulating autophagy and cell metabolism can be a promising therapeutic strategy for OC treatment. Resveratrol has emerged as a possible anticancer treatment because it induces autophagy and modulates metabolism through multiple molecular signaling pathways. However, autophagy dysregulation enhances tumor cell growth by continuously providing nutrients. Given the complexity of the metabolic processes upregulated and/or downregulated within the TME in relation to cancer status and their tight interconnections, targeting metabolism is of great importance for treating cancer. Additionally, combining autophagy/metabolic targeted therapy with conventional therapies such as cisplatin can show strong beneficial outcomes in patients with OC. In conclusion, elucidating the autophagic process and regulation of metabolism may lead to precise strategies for OC treatment.

Author Contributions

Conceptualization—MP, SC, MS, and HY; writing - original draft preparation—MP, SC, MS, AK, KM, HK, and HY; writing - review and editing—MP, SC, MS, AK, KM, HK, and HY; supervision—HY; funding acquisition—HY; all authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by Brain Korea 21 (BK21; # M2022B002600003).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biology & Medicine. 2017; 14: 9–32.

[2] Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet. 2014; 384: 1376–1388.

[3] Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, *et al*. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2021; 19: 77–102.

[4] Hollis RL, Croy I, Churchman M, Bartos C, Rye T, Gourley C, *et al*. Ovarian carcinosarcoma is a distinct form of ovarian cancer with poorer survival compared to tubo-ovarian high-grade serous carcinoma. British Journal of Cancer. 2022; 127: 1034–1042.

[5] Stewart C, Ralyea C, Lockwood S. Ovarian Cancer: An Integrated Review. Seminars in Oncology Nursing. 2019; 35: 151–156.

[6] Zhang B, Cai FF, Zhong XY. An overview of biomarkers for the ovarian cancer diagnosis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2011; 158: 119–123.

[7] Dieplinger H, Ankerst DP, Burges A, Lenhard M, Lingenhel A, Fineder L, *et al*. Afamin and apolipoprotein A-IV: novel protein markers for ovarian cancer. Cancer Epidemiology, Biomarkers & Prevention. 2009; 18: 1127–1133.

[8] Ryu J, Thomas SN. Quantitative Mass Spectrometry-Based Proteomics for Biomarker Development in Ovarian Cancer. Molecules. 2021; 26: 2674.

[9] Forstner R. Early detection of ovarian cancer. European Radiology. 2020; 30: 5370–5373.

[10] Baci D, Bosi A, Gallazzi M, Rizzi M, Noonan DM, Poggi A, *et al*. The Ovarian Cancer Tumor Immune Microenvironment (TIME) as Target for Therapy: A Focus on Innate Immunity Cells as Therapeutic Effectors. International Journal of Molecular Sciences. 2020; 21: 3125.

[11] Lengyel E. Ovarian cancer development and metastasis. The American Journal of Pathology. 2010; 177: 1053–1064.

[12] Thiery JP, Sleeman JP. Complex networks orchestrate epithelial-mesenchymal transitions. Nature Reviews. Molecular Cell Biology. 2006; 7: 131–142.

[13] Thiery JP, Acloque H, Huang RYJ, Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell. 2009; 139: 871–890.

[14] Roane BM, Arend RC, Birrer MJ. Review: Targeting the Transforming Growth Factor-Beta Pathway in Ovarian Cancer. Cancers. 2019; 11: 668.

[15] Perez-Fidalgo JA, Ortega B, Simon S, Samartzis EP, Boussios S. NOTCH signalling in ovarian cancer angiogenesis. Annals of Translational Medicine. 2020; 8: 1705.

[16] Teeuwssen M, Fodde R. Wnt Signaling in Ovarian Cancer Stemness, EMT, and Therapy Resistance. Journal of Clinical Medicine. 2019; 8: 1658.
[17] Ediriweera MK, Tennekoon KH, Samarakoon SR. Role of the PI3K/AKT/mTOR signaling pathway in ovarian cancer: Biological and therapeutic significance. Seminars in Cancer Biology. 2019; 59: 147–160.
[18] Yun CW, Lee SH. The Roles of Autophagy in Cancer. International Journal of Molecular Sciences. 2018; 19: 3466.
[19] Yonekawa T, Thorburn A. Autophagy and cell death. Essays in Biochemistry. 2013; 55: 105–117.
[20] Yim WWY, Mizushima N. Lysosome biology in autophagy. Cell Discovery. 2020; 6: 6.
[21] Verma AK, Bharti PS, Rafat S, Bhatt D, Goyal Y, Pandey KK, *et al*. Autophagy Paradox of Cancer: Role, Regulation, and Duality. Oxidative Medicine and Cellular Longevity. 2021; 2021: 8832541.
[22] Liang C, Jung JU. Autophagy genes as tumor suppressors. Current Opinion in Cell Biology. 2010; 22: 226–233.
[23] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646–674.
[24] Pavlova NN, Zhu J, Thompson CB. The hallmarks of cancer metabolism: Still emerging. Cell Metabolism. 2022; 34: 355–377.
[25] Hurley JH, Young LN. Mechanisms of Autophagy Initiation. Annual Review of Biochemistry. 2017; 86: 225–244.
[26] Zhao YG, Zhang H. Autophagosome maturation: An epic journey from the ER to lysosomes. The Journal of Cell Biology. 2019; 218: 757–770.
[27] Moreau K, Renna M, Rubinsztein DC. Connections between SNAREs and autophagy. Trends in Biochemical Sciences. 2013; 38: 57–63.
[28] Reggiori F, Ungermann C. Autophagosome Maturation and Fusion. Journal of Molecular Biology. 2017; 429: 486–496.
[29] Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell. 2011; 147: 728–741.
[30] Hikita H, Sakane S, Takehara T. Mechanisms of the autophagosome-lysosome fusion step and its relation to non-alcoholic fatty liver disease. Liver Research. 2018; 2: 120–124.
[31] Tanaka S, Hikita H, Tatsumi T, Sakamori R, Nozaki Y, Sakane S, *et al*. Rubicon inhibits autophagy and accelerates hepatocyte apoptosis and lipid accumulation in nonalcoholic fatty liver disease in mice. Hepatology. 2016; 64: 1994–2014.
[32] Wang C, Wang H, Zhang D, Luo W, Liu R, Xu D, *et al*. Phosphorylation of ULK1 affects autophagosome fusion and links chaperone-mediated autophagy to macroautophagy. Nature Communications. 2018; 9: 3492.
[33] Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nature Cell Biology. 2011; 13: 132–141.
[34] Menon MB, Dhamija S. Beclin 1 Phosphorylation - at the Center of Autophagy Regulation. Frontiers in Cell and Developmental Biology. 2018; 6: 137.
[35] Chavez-Dominguez R, Perez-Medina M, Lopez-Gonzalez JS, Galicia-Velasco M, Aguilar-Cazares D. The Double-Edge Sword of Autophagy in Cancer: From Tumor Suppression to Pro-tumor Activity. Frontiers in Oncology. 2020; 10: 578418.
[36] Galluzzi L, Pietrocola F, Bravo-San Pedro JM, Amaravadi RK, Baehrecke EH, Cecconi F, *et al*. Autophagy in malignant transformation and cancer progression. The EMBO Journal. 2015; 34: 856–880.
[37] Kisen GO, Tessitore L, Costelli P, Gordon PB, Schwarze PE, Baccino FM, *et al*. Reduced autophagic activity in primary rat hepatocellular carcinoma and ascites hepatoma cells. Carcinogenesis. 1993; 14: 2501–2505.
[38] LoPiccolo J, Blumenthal GM, Bernstein WB, Dennis PA. Targeting the PI3K/Akt/mTOR pathway: effective combinations and clinical considerations. Drug Resistance Updates: Reviews and Commentaries in Antimicrobial and Anticancer Chemotherapy. 2008; 11: 32–50.
[39] Towers CG, Wodetzki D, Thorburn A. Autophagy and cancer: Modulation of cell death pathways and cancer cell adaptations. The Journal of Cell Biology. 2020; 219: e201909033.
[40] Laddha SV, Ganesan S, Chan CS, White E. Mutational landscape of the essential autophagy gene BECN1 in human cancers. Molecular Cancer Research. 2014; 12: 485–490.
[41] Yang ZJ, Chee CE, Huang S, Sinicrope FA. The role of autophagy in cancer: therapeutic implications. Molecular Cancer Therapeutics. 2011; 10: 1533–1541.
[42] Bhatt V, Khayati K, Hu ZS, Lee A, Kamran W, Su X, *et al*. Autophagy modulates lipid metabolism to maintain metabolic flexibility for Lkb1-deficient Kras-driven lung tumorigenesis. Genes & Development. 2019; 33: 150–165.
[43] Chen HT, Liu H, Mao MJ, Tan Y, Mo XQ, Meng XJ, *et al*. Crosstalk between autophagy and epithelial-mesenchymal transition and its application in cancer therapy. Molecular Cancer. 2019; 18: 101.
[44] Gundamaraju R, Lu W, Paul MK, Jha NK, Gupta PK, Ojha S, *et al*. Autophagy and EMT in cancer and metastasis: Who controls whom? Biochimica et Biophysica Acta. Molecular Basis of Disease. 2022; 1868: 166431.
[45] Abdel-Wahab AF, Mahmoud W, Al-Harizy RM. Targeting glucose metabolism to suppress cancer progression: prospective of anti-glycolytic cancer therapy. Pharmacological Research. 2019; 150: 104511.
[46] Wei Z, Liu X, Cheng C, Yu W, Yi P. Metabolism of Amino Acids in Cancer. Frontiers in Cell and Developmental Biology. 2021; 8: 603837.
[47] Muhammad N, Lee HM, Kim J. Oncology Therapeutics Targeting the Metabolism of Amino Acids. Cells. 2020; 9: 1904.
[48] Ananieva EA, Wilkinson AC. Branched-chain amino acid metabolism in cancer. Current Opinion in Clinical Nutrition and Metabolic Care. 2018; 21: 64–70.
[49] Sivanand S, Vander Heiden MG. Emerging Roles for Branched-Chain Amino Acid Metabolism in Cancer. Cancer Cell. 2020; 37: 147–156.
[50] Duan Y, Li F, Li Y, Tang Y, Kong X, Feng Z, *et al*. The role of leucine and its metabolites in protein and energy metabolism. Amino Acids. 2016; 48: 41–51.
[51] Saxton RA, Knockenhauer KE, Wolfson RL, Chantranupong L, Pacold ME, Wang T, *et al*. Structural basis for leucine sensing by the Sestrin2-mTORC1 pathway. Science. 2016; 351: 53–58.
[52] Wolfson RL, Chantranupong L, Saxton RA, Shen K, Scaria SM, Cantor JR, *et al*. Sestrin2 is a leucine sensor for the mTORC1 pathway. Science. 2016; 351: 43–48.
[53] Lieu EL, Nguyen T, Rhyne S, Kim J. Amino acids in cancer. Experimental & Molecular Medicine. 2020; 52: 15–30.
[54] Lee JH, Cho YR, Kim JH, Kim J, Nam HY, Kim SW, *et al*. Branched-chain amino acids sustain pancreatic cancer growth by regulating lipid metabolism. Experimental & Molecular Medicine. 2019; 51: 1–11.
[55] Choi BH, Coloff JL. The Diverse Functions of Non-Essential Amino Acids in Cancer. Cancers. 2019; 11: 675.
[56] Wise DR, Thompson CB. Glutamine addiction: a new therapeutic target in cancer. Trends in Biochemical Sciences. 2010; 35: 427–433.
[57] Choi YK, Park KG. Targeting Glutamine Metabolism for Cancer Treatment. Biomolecules & Therapeutics. 2018; 26: 19–28.
[58] Santos CR, Schulze A. Lipid metabolism in cancer. The FEBS Journal. 2012; 279: 2610–2623.
[59] Maan M, Peters JM, Dutta M, Patterson AD. Lipid metabolism

and lipophagy in cancer. Biochemical and Biophysical Research Communications. 2018; 504: 582–589.
[60] Luo X, Cheng C, Tan Z, Li N, Tang M, Yang L, *et al*. Emerging roles of lipid metabolism in cancer metastasis. Molecular Cancer. 2017; 16: 76.
[61] Zhang F, Du G. Dysregulated lipid metabolism in cancer. World Journal of Biological Chemistry. 2012; 3: 167–174.
[62] Fernández LP, Gómez de Cedrón M, Ramírez de Molina A. Alterations of Lipid Metabolism in Cancer: Implications in Prognosis and Treatment. Frontiers in Oncology. 2020; 10: 577420.
[63] Peracchio C, Alabiso O, Valente G, Isidoro C. Involvement of autophagy in ovarian cancer: a working hypothesis. Journal of Ovarian Research. 2012; 5: 22.
[64] Shen Y, Li DD, Wang LL, Deng R, Zhu XF. Decreased expression of autophagy-related proteins in malignant epithelial ovarian cancer. Autophagy. 2008; 4: 1067–1068.
[65] Liang XH, Jackson S, Seaman M, Brown K, Kempkes B, Hibshoosh H, *et al*. Induction of autophagy and inhibition of tumorigenesis by beclin 1. Nature. 1999; 402: 672–676.
[66] Kolasa IK, Rembiszewska A, Janiec-Jankowska A, Dansonka-Mieszkowska A, Lewandowska AM, Konopka B, *et al*. PTEN mutation, expression and LOH at its locus in ovarian carcinomas. Relation to TP53, K-RAS and BRCA1 mutations. Gynecologic Oncology. 2006; 103: 692–697.
[67] Tasdemir E, Maiuri MC, Galluzzi L, Vitale I, Djavaheri-Mergny M, D'Amelio M, *et al*. Regulation of autophagy by cytoplasmic p53. Nature Cell Biology. 2008; 10: 676–687.
[68] Anderson NM, Simon MC. The tumor microenvironment. Current Biology. 2020; 30: R921–R925.
[69] Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nature Reviews. Cancer. 2009; 9: 798–809.
[70] Yoshida M, Taguchi A, Kawana K, Ogishima J, Adachi K, Kawata A, *et al*. Intraperitoneal neutrophils activated by KRAS-induced ovarian cancer exert antitumor effects by modulating adaptive immunity. International Journal of Oncology. 2018; 53: 1580–1590.
[71] Gardini A, Baillat D, Cesaroni M, Shiekhattar R. Genome-wide analysis reveals a role for BRCA1 and PALB2 in transcriptional co-activation. The EMBO Journal. 2014; 33: 890–905.
[72] Thuwajit C, Ferraresi A, Titone R, Thuwajit P, Isidoro C. The metabolic cross-talk between epithelial cancer cells and stromal fibroblasts in ovarian cancer progression: Autophagy plays a role. Medicinal Research Reviews. 2018; 38: 1235–1254.
[73] Ferraresi A, Phadngam S, Morani F, Galetto A, Alabiso O, Chiorino G, *et al*. Resveratrol inhibits IL-6-induced ovarian cancer cell migration through epigenetic up-regulation of autophagy. Molecular Carcinogenesis. 2017; 56: 1164–1181.
[74] Yan Y, Chen X, Wang X, Zhao Z, Hu W, Zeng S, *et al*. The effects and the mechanisms of autophagy on the cancer-associated fibroblasts in cancer. Journal of Experimental & Clinical Cancer Research: CR. 2019; 38: 171.
[75] Chou CH, Wei LH, Kuo ML, Huang YJ, Lai KP, Chen CA, *et al*. Up-regulation of interleukin-6 in human ovarian cancer cell via a Gi/PI3K-Akt/NF-kappaB pathway by lysophosphatidic acid, an ovarian cancer-activating factor. Carcinogenesis. 2005; 26: 45–52.
[76] Chang CL, Liao JJ, Huang WP, Lee H. Lysophosphatidic acid inhibits serum deprivation-induced autophagy in human prostate cancer PC-3 cells. Autophagy. 2007; 3: 268–270.
[77] Goldsmith J, Levine B, Debnath J. Autophagy and cancer metabolism. Methods in Enzymology. 2014; 542: 25–57.
[78] Tan AS, Baty JW, Dong LF, Bezawork-Geleta A, Endaya B, Goodwin J, *et al*. Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA. Cell Metabolism. 2015; 21: 81–94.
[79] Rocchi A, He C. Emerging roles of autophagy in metabolism and metabolic disorders. Frontiers in Biology. 2015; 10: 154–164.
[80] King KE, Losier TT, Russell RC. Regulation of Autophagy Enzymes by Nutrient Signaling. Trends in Biochemical Sciences. 2021; 46: 687–700.
[81] Rabinowitz JD, White E. Autophagy and metabolism. Science. 2010; 330: 1344–1348.
[82] Chang C, Su H, Zhang D, Wang Y, Shen Q, Liu B, *et al*. AMPK-Dependent Phosphorylation of GAPDH Triggers Sirt1 Activation and Is Necessary for Autophagy upon Glucose Starvation. Molecular Cell. 2015; 60: 930–940.
[83] Roberts DJ, Tan-Sah VP, Ding EY, Smith JM, Miyamoto S. Hexokinase-II positively regulates glucose starvation-induced autophagy through TORC1 inhibition. Molecular Cell. 2014; 53: 521–533.
[84] Ha JH, Radhakrishnan R, Jayaraman M, Yan M, Ward JD, Fung KM, *et al*. LPA Induces Metabolic Reprogramming in Ovarian Cancer via a Pseudohypoxic Response. Cancer Research. 2018; 78: 1923–1934.
[85] Gerald D, Berra E, Frapart YM, Chan DA, Giaccia AJ, Mansuy D, *et al*. JunD reduces tumor angiogenesis by protecting cells from oxidative stress. Cell. 2004; 118: 781–794.
[86] Hay N. Reprogramming glucose metabolism in cancer: can it be exploited for cancer therapy? Nature Reviews. Cancer. 2016; 16: 635–649.
[87] Murugan AK. mTOR: Role in cancer, metastasis and drug resistance. Seminars in Cancer Biology. 2019; 59: 92–111.
[88] Hara K, Yonezawa K, Weng QP, Kozlowski MT, Belham C, Avruch J. Amino acid sufficiency and mTOR regulate p70 S6 kinase and eIF-4E BP1 through a common effector mechanism. The Journal of Biological Chemistry. 1998; 273: 14484–14494.
[89] Yang L, Moss T, Mangala LS, Marini J, Zhao H, Wahlig S, *et al*. Metabolic shifts toward glutamine regulate tumor growth, invasion and bioenergetics in ovarian cancer. Molecular Systems Biology. 2014; 10: 728.
[90] Eng CH, Yu K, Lucas J, White E, Abraham RT. Ammonia derived from glutaminolysis is a diffusible regulator of autophagy. Science Signaling. 2010; 3: ra31.
[91] Yang L, Venneti S, Nagrath D. Glutaminolysis: A Hallmark of Cancer Metabolism. Annual Review of Biomedical Engineering. 2017; 19: 163–194.
[92] Cheong H, Lindsten T, Wu J, Lu C, Thompson CB. Ammonia-induced autophagy is independent of ULK1/ULK2 kinases. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 11121–11126.
[93] Baracco EE, Castoldi F, Durand S, Enot DP, Tadic J, Kainz K, *et al*. α-Ketoglutarate inhibits autophagy. Aging. 2019; 11: 3418–3431.
[94] Al-Koussa H, El Mais N, Maalouf H, Abi-Habib R, El-Sibai M. Arginine deprivation: a potential therapeutic for cancer cell metastasis? A review. Cancer Cell International. 2020; 20: 150.
[95] Szlosarek PW. Arginine deprivation and autophagic cell death in cancer. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111: 14015–14016.
[96] Nicklin P, Bergman P, Zhang B, Triantafellow E, Wang H, Nyfeler B, *et al*. Bidirectional transport of amino acids regulates mTOR and autophagy. Cell. 2009; 136: 521–534.
[97] Kroemer G, Mariño G, Levine B. Autophagy and the integrated stress response. Molecular Cell. 2010; 40: 280–293.
[98] Shuvayeva G, Bobak Y, Igumentseva N, Titone R, Morani F, Stasyk O, *et al*. Single amino acid arginine deprivation triggers prosurvival autophagic response in ovarian carcinoma SKOV3. BioMed Research International. 2014; 2014: 505041.
[99] Ben-Sahra I, Manning BD. mTORC1 signaling and the metabolic control of cell growth. Current Opinion in Cell Biology. 2017; 45: 72–82.

[100] Groenewoud MJ, Zwartkruis FJT. Rheb and Rags come together at the lysosome to activate mTORC1. Biochemical Society Transactions. 2013; 41: 951–955.
[101] Bar-Peled L, Schweitzer LD, Zoncu R, Sabatini DM. Ragulator is a GEF for the rag GTPases that signal amino acid levels to mTORC1. Cell. 2012; 150: 1196–1208.
[102] Chantranupong L, Scaria SM, Saxton RA, Gygi MP, Shen K, Wyant GA, *et al*. The CASTOR Proteins Are Arginine Sensors for the mTORC1 Pathway. Cell. 2016; 165: 153–164.
[103] Wilden AR, Molina JA, Feuerborn M, Boyle D, Lee SY. Glutamine-dependent lysosome homeostatic changes induced by starvation and lysosome inhibition. Biochimica et Biophysica Acta. Molecular Cell Research. 2018; 1865: 1356–1367.
[104] Shin DW. Lipophagy: Molecular Mechanisms and Implications in Metabolic Disorders. Molecules and Cells. 2020; 43: 686–693.
[105] Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, *et al*. Autophagy regulates lipid metabolism. Nature. 2009; 458: 1131–1135.
[106] Tan Y, Li J, Zhao G, Huang KC, Cardenas H, Wang Y, *et al*. Metabolic reprogramming from glycolysis to fatty acid uptake and beta-oxidation in platinum-resistant cancer cells. Nature Communications. 2022; 13: 4554.
[107] Li Z, Liu H, Luo X. Lipid droplet and its implication in cancer progression. American Journal of Cancer Research. 2020; 10: 4112–4122.
[108] Lettieri Barbato D, Tatulli G, Aquilano K, Ciriolo MR. FoxO1 controls lysosomal acid lipase in adipocytes: implication of lipophagy during nutrient restriction and metformin treatment. Cell Death & Disease. 2013; 4: e861.
[109] Qu P, Du H, Wilkes DS, Yan C. Critical roles of lysosomal acid lipase in T cell development and function. The American Journal of Pathology. 2009; 174: 944–956.
[110] Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. Regulation of tumor metastasis by myeloid-derived suppressor cells. Annual Review of Medicine. 2015; 66: 97–110.
[111] Du H, Zhao T, Ding X, Yan C. Hepatocyte-Specific Expression of Human Lysosome Acid Lipase Corrects Liver Inflammation and Tumor Metastasis in lal(-/-) Mice. The American Journal of Pathology. 2015; 185: 2379–2389.
[112] Rodriguez GM, Galpin KJC, McCloskey CW, Vanderhyden BC. The Tumor Microenvironment of Epithelial Ovarian Cancer and Its Influence on Response to Immunotherapy. Cancers. 2018; 10: 242.
[113] Yang Y, Yang Y, Yang J, Zhao X, Wei X. Tumor Microenvironment in Ovarian Cancer: Function and Therapeutic Strategy. Frontiers in Cell and Developmental Biology. 2020; 8: 758.
[114] Drakes ML, Stiff PJ. Regulation of Ovarian Cancer Prognosis by Immune Cells in the Tumor Microenvironment. Cancers. 2018; 10: 302.
[115] Musacchio L, Cicala CM, Camarda F, Ghizzoni V, Giudice E, Carbone MV, *et al*. Combining PARP inhibition and immune checkpoint blockade in ovarian cancer patients: a new perspective on the horizon? ESMO Open. 2022; 7: 100536.
[116] Aquila S, Santoro M, Caputo A, Panno ML, Pezzi V, De Amicis F. The Tumor Suppressor PTEN as Molecular Switch Node Regulating Cell Metabolism and Autophagy: Implications in Immune System and Tumor Microenvironment. Cells. 2020; 9: 1725.
[117] Leary A, Tan D, Ledermann J. Immune checkpoint inhibitors in ovarian cancer: where do we stand? Therapeutic Advances in Medical Oncology. 2021; 13: 17588359211039899.
[118] Vidotto T, Melo CM, Castelli E, Koti M, Dos Reis RB, Squire JA. Emerging role of PTEN loss in evasion of the immune response to tumours. British Journal of Cancer. 2020; 122: 1732–1743.
[119] Gao T, Zhang X, Zhao J, Zhou F, Wang Y, Zhao Z, *et al*. SIK2 promotes reprogramming of glucose metabolism through PI3K/AKT/HIF-1α pathway and Drp1-mediated mitochondrial fission in ovarian cancer. Cancer Letters. 2020; 469: 89–101.
[120] Ortega-Molina A, Serrano M. PTEN in cancer, metabolism, and aging. Trends in Endocrinology and Metabolism. 2013; 24: 184–189.
[121] Phadngam S, Castiglioni A, Ferraresi A, Morani F, Follo C, Isidoro C. PTEN dephosphorylates AKT to prevent the expression of GLUT1 on plasmamembrane and to limit glucose consumption in cancer cells. Oncotarget. 2016; 7: 84999–85020.
[122] Martin de la Fuente L, Westbom-Fremer S, Arildsen NS, Hartman L, Malander S, Kannisto P, *et al*. PD-1/PD-L1 expression and tumor-infiltrating lymphocytes are prognostically favorable in advanced high-grade serous ovarian carcinoma. Virchows Archiv. 2020; 477: 83–91.
[123] Clark CA, Gupta HB, Sareddy G, Pandeswara S, Lao S, Yuan B, *et al*. Tumor-Intrinsic PD-L1 Signals Regulate Cell Growth, Pathogenesis, and Autophagy in Ovarian Cancer and Melanoma. Cancer Research. 2016; 76: 6964–6974.
[124] Gao H, Zhang J, Ren X. PD-L1 regulates tumorigenesis and autophagy of ovarian cancer by activating mTORC signaling. Bioscience Reports. 2019; 39: BSR20191041.
[125] Kao C, Chao A, Tsai CL, Chuang WC, Huang WP, Chen GC, *et al*. Bortezomib enhances cancer cell death by blocking the autophagic flux through stimulating ERK phosphorylation. Cell Death & Disease. 2014; 5: e1510.
[126] Zhao X, Fang Y, Yang Y, Qin Y, Wu P, Wang T, *et al*. Elaiophylin, a novel autophagy inhibitor, exerts antitumor activity as a single agent in ovarian cancer cells. Autophagy. 2015; 11: 1849–1863.
[127] Zi D, Zhou ZW, Yang YJ, Huang L, Zhou ZL, He SM, *et al*. Danusertib Induces Apoptosis, Cell Cycle Arrest, and Autophagy but Inhibits Epithelial to Mesenchymal Transition Involving PI3K/Akt/mTOR Signaling Pathway in Human Ovarian Cancer Cells. International Journal of Molecular Sciences. 2015; 16: 27228–27251.
[128] Xie Q, Chen Y, Tan H, Liu B, Zheng LL, Mu Y. Targeting Autophagy with Natural Compounds in Cancer: A Renewed Perspective from Molecular Mechanisms to Targeted Therapy. Frontiers in Pharmacology. 2021; 12: 748149.
[129] Galli U, Colombo G, Travelli C, Tron GC, Genazzani AA, Grolla AA. Recent Advances in NAMPT Inhibitors: A Novel Immunotherapic Strategy. Frontiers in Pharmacology. 2020; 11: 656.
[130] Lin ZP, Zhu YL, Lo YC, Moscarelli J, Xiong A, Korayem Y, *et al*. Combination of triapine, olaparib, and cediranib suppresses progression of BRCA-wild type and PARP inhibitor-resistant epithelial ovarian cancer. PLoS ONE. 2018; 13: e0207399.
[131] Roche M, Parisi L, Li L, Knehans A, Phaeton R, Kesterson JP. The role of pemetrexed in recurrent epithelial ovarian cancer: A scoping review. Oncology Reviews. 2018; 12: 346.
[132] Romagnoli A, Maracci C, D'Agostino M, Teana AL, Marino DD. Targeting mTOR and eIF4E: a feasible scenario in ovarian cancer therapy. Cancer Drug Resistance. 2021; 4: 596–606.
[133] Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012; 149: 274–293.
[134] Pokhriyal R, Hariprasad R, Kumar L, Hariprasad G. Chemotherapy Resistance in Advanced Ovarian Cancer Patients. Biomarkers in Cancer. 2019; 11: 1179299X19860815.
[135] Boussios S, Rassy E, Moschetta M, Ghose A, Adeleke S, Sanchez E, *et al*. BRCA Mutations in Ovarian and Prostate Cancer: Bench to Bedside. Cancers. 2022; 14: 3888.
[136] Van Nyen T, Planque M, van Wagensveld L, Duarte JAG, Zaal EA, Talebi A, *et al*. Serine metabolism remodeling after platinum-based chemotherapy identifies vulnerabilities in a

subgroup of resistant ovarian cancers. Nature Communications. 2022; 13: 4578.

[137] Sociali G, Raffaghello L, Magnone M, Zamporlini F, Emionite L, Sturla L, *et al*. Antitumor effect of combined NAMPT and CD73 inhibition in an ovarian cancer model. Oncotarget. 2016; 7: 2968–2984.

[138] Ratner ES, Zhu YL, Penketh PG, Berenblum J, Whicker ME, Huang PH, *et al*. Triapine potentiates platinum-based combination therapy by disruption of homologous recombination repair. British Journal of Cancer. 2016; 114: 777–786.

[139] Wallace-Povirk A, Hou Z, Nayeen MJ, Gangjee A, Matherly LH. Folate Transport and One-Carbon Metabolism in Targeted Therapies of Epithelial Ovarian Cancer. Cancers. 2021; 14: 191.

[140] Egloff H, Jatoi A. Pemetrexed for ovarian cancer: a systematic review of the published literature and a consecutive series of patients treated in a nonclinical trial setting. Case Reports in Oncology. 2014; 7: 541–549.

[141] De Vitto H, Arachchige DB, Richardson BC, French JB. The Intersection of Purine and Mitochondrial Metabolism in Cancer. Cells. 2021; 10: 2603.

[142] Mukhopadhyay S, Mahapatra KK, Praharaj PP, Patil S, Bhutia SK. Recent progress of autophagy signaling in tumor microenvironment and its targeting for possible cancer therapeutics. Seminars in Cancer Biology. 2022; 85: 196–208.

[143] Siu MKY, Jiang YX, Wang JJ, Leung THY, Han CY, Tsang BK, *et al*. Hexokinase 2 Regulates Ovarian Cancer Cell Migration, Invasion and Stemness via FAK/ERK1/2/MMP9/NANOG/SOX9 Signaling Cascades. Cancers. 2019; 11: 813.

[144] Kueck A, Opipari AW, Jr, Griffith KA, Tan L, Choi M, Huang J, *et al*. Resveratrol inhibits glucose metabolism in human ovarian cancer cells. Gynecologic Oncology. 2007; 107: 450–457.

[145] Han CY, Patten DA, Richardson RB, Harper ME, Tsang BK. Tumor metabolism regulating chemosensitivity in ovarian cancer. Genes & Cancer. 2018; 9: 155–175.

[146] Tan L, Wang W, He G, Kuick RD, Gossner G, Kueck AS, *et al*. Resveratrol inhibits ovarian tumor growth in an in vivo mouse model. Cancer. 2016; 122: 722–729.

[147] Rauf A, Imran M, Butt MS, Nadeem M, Peters DG, Mubarak MS. Resveratrol as an anti-cancer agent: A review. Critical Reviews in Food Science and Nutrition. 2018; 58: 1428–1447.

[148] Wu SX, Xiong RG, Huang SY, Zhou DD, Saimaiti A, Zhao CN, *et al*. Effects and mechanisms of resveratrol for prevention and management of cancers: An updated review. Critical Reviews in Food Science and Nutrition. 2022. (online ahead of print)

[149] Muhanmode Y, Wen MK, Maitinuri A, Shen G. Curcumin and resveratrol inhibit chemoresistance in cisplatin-resistant epithelial ovarian cancer cells via targeting P13K pathway. Human & Experimental Toxicology. 2022; 41: 9603271221095929.