Adaptation mechanisms in cancer: Lipid metabolism under hypoxia and nutrient deprivation as a target for novel therapeutic strategies (Review)

SHIRO KOIZUME[1,2] and YOHEI MIYAGI[1,2]

[1]Molecular Pathology and Genetics Division, Kanagawa Cancer Center Research Institute, Yokohama, Kanagawa 241-8515, Japan; [2]Department of Pathology, Kanagawa Cancer Center Hospital, Yokohama, Kanagawa 241-8515, Japan

Received October 30, 2024; Accepted January 3, 2025

DOI: 10.3892/mmr.2025.13448

Correspondence to: Dr Shiro Koizume, Molecular Pathology and Genetics Division, Kanagawa Cancer Center Research Institute, 2-3-2 Nakao, Asahi, Yokohama, Kanagawa 241-8515, Japan
E-mail: koizume.2230b@kanagawa-pho.jp

Abbreviations: AA, amino acid; ACC1, acetyl-CoA carboxylase 1; ACLY, ATP citrate lyase; AD, arginine deficiency; AMPK, AMP-activated protein kinase; ASS1, argininosuccinate synthetase 1; ARNT, aryl hydrocarbon receptor nuclear translocator; ATGL, adipose triglyceride lipase; ATM, ataxia-telangiectasia mutated; ATP, adenosine triphosphate; CAF, cancer-associated fibroblast; CBS, cystathionine β-synthase; ccRCC, clear cell renal cell carcinoma; CD, cysteine deficiency; CD36, cluster of differentiation 36; CHTM1, coiled-coil helix tumor and metabolism 1; CHKα2, choline kinase α2; CISD3, CDGSH iron sulfur domain 3; c-Myc, MYC proto-oncogene, bHLH transcription factor; CPT2, carnitine palmitoyltransferase 2; CREB, CRE-binding protein; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; FA, fatty acid; FABP, fatty acid binding protein; FAO, fatty acid oxidation; FAS, fatty acid synthase; FOXM1, forkhead box M1; FPN1, ferroportin; GD, glucose deficiency; GILZ, glucocorticoid-induced leucine zipper; GlnD, glutamine deficiency; GSH, glutathione; GSK3β, glycogen synthase kinase 3β; HGD, hypoxia and glucose deficiency; HRD1, HMG-CoA reductase degradation protein 1; HIF, hypoxia-inducible factor; IRE1, inositol-requiring protein 1; LCFA, long-chain fatty acid; LD, lipid droplet; LPO, lipid peroxidation; LRP1, lipoprotein receptor-related protein 1; MD, methionine deficiency; MTF1, metal regulatory transcription factor 1; mTOR, mammalian target of rapamycin; NRF2, nuclear factor-erythroid 2-related factor-2; OCCC, ovarian clear cell carcinoma; PEPCK-M, phosphoenolpyruvate carboxykinase-M; PERK, PKR-like ER kinase; 3-PG, 3-phosphoglycerate; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; PGM1, phosphoglucomutase 1; PHGDH, phosphoglycerate dehydrogenase; PI3K-C2γ, phosphoinositide 3-kinase-C2γ; PIM1, proviral integration site for Moloney murine leukemia virus 1; PKC, protein kinase C; PLD1, phospholipase D1; POX, proline oxidase; PPARα, peroxisome proliferator-activated receptor α; Sp1, specificity protein 1; SREBP1, sterol regulatory element binding protein-1; SREBP2, sterol regulatory element binding protein-2; SSH, serum starvation and hypoxia; SCD5, stearoyl-CoA desaturase 5; SGD, serine/glycine deficiency; TRIAP-1, TP53-regulated inhibitor of apoptosis 1; UPR, unfolded protein response; VHL, von Hippel Lindau

Key words: cancer, lipid metabolism, hypoxia, glucose deprivation, amino acid deprivation

Abstract. Tumor tissues generally exist in a relatively hypovascular state, and cancer cells must adapt to severe tissue conditions with a limited molecular oxygen and nutrient supply for their survival. Lipid metabolism serves a role in this adaptation. Lipids are supplied not only through the bloodstream but also through autonomous synthesis by cancer cells, and they function as sources of adenosine triphosphate and cell components. Although cancer-associated lipid metabolism has been widely reviewed, how this metabolism responds to the tumor environment with poor molecular oxygen and nutrient supply remains to be fully discussed. The main aim of the present review was to summarize the findings on this issue and to provide insights into how cancer cells adapt to better cope with metabolic stresses within tumors. It may be suggested that diverse types of lipid metabolism have a role in enabling cancer cells to adapt to both hypoxia and nutrient-poor conditions. Gaining a deeper understanding of these molecular mechanisms may reveal novel possibilities of exploration for cancer treatment.

Contents

1. Introduction

Cancer is a complex disease involving multiple steps for the transition from a normal state to a neoplastic growth state, followed by the generation of malignant cells. The 'hallmarks of cancer' concept encompasses 14 elements required for this process in human cancers (1), and metabolic reprogramming is one of these elements (1,2). Several characteristic metabolic mechanisms involving glucose and amino acids (AAs) in cancer cells have

been revealed, and new insights continue to emerge (2). Tumor tissues are exposed to stress through insufficient supply of molecular oxygen and nutrients (3). Cancer cells must adapt to these severe environmental conditions and change their mechanisms for energy acquisition and immune evasion to achieve progression (3). A recent review has revealed that metabolic crosstalk between cancer cells and tumor stromal cells, including immune cells and fibroblasts, can promote symbiosis and malignancy (3).

Since the discovery of the Warburg effect, glucose has been regarded as a primary nutrient for cancer cells through aerobic glycolysis (2). However, this adenosine triphosphate (ATP) production pathway is not always predominant because oxidative phosphorylation remains active in many cancer cells (2). Recent studies have shown that cancer cells utilize glutamine and lipids not only as ATP sources but also as precursors of plasma membrane components and lipid droplets (LDs) (4,5). Regarding lipids, long-chain fatty acids (LCFAs) are energy sources and precursors of various phospholipids (5,6). Indeed, endogenously and exogenously supplied fatty acids (FAs) are sources for ATP production in cancer cells via oxidative phosphorylation (5,6). Although cholesterol is not an energy source, it is important for plasma membrane function, steroid hormone generation, and cellular signaling (6).

Several studies have suggested that lipid metabolism has potential as a therapeutic target in cancer treatment (4-6). A recent study further revealed that inhibition of ATP citrate lyase (ACLY), which is responsible for production of acetyl-CoA, a lipogenesis precursor, can overcome cancer immunotherapy resistance (7). Fatty acid synthase (FAS), which is generally responsible for lipogenesis, can contribute to many aspects of cancer progression (8). An intermediate compound of cholesterol biosynthesis, 7-dehydrocholesterol, can act as a natural inhibitor of ferroptosis in multiple cancer cells (9,10). Thus, the development of new therapeutic strategies targeting these various forms of lipid metabolism is ongoing.

Hypoxia is a general condition in tumors that limits the availability of not only molecular oxygen but also glucose, AAs, and/or lipids from the bloodstream depending on the tumor's distance from the vasculature (11,12) (Fig. 1). Deficiency of these elements in tumors is likely accelerated by the high catabolic demand of cancer cells and vascular immaturity. Therefore, adaptation to these harsh conditions is essential for cancer progression. However, the published relationships among hypoxia, glucose deficiency, AA deficiency, and lipid deficiency in cancer cells have been poorly integrated. A therapeutic strategy targeting these harsh tissue conditions may be beneficial because they are expected to be characteristic of tumors, and such therapy is thus likely to mitigate the toxic adverse effects associated with other therapeutic approaches. The objective of the present review is to summarize the latest understanding on this topic, with a particular focus on lipid metabolism. The review mainly aims to provide a comprehensive perspective on how cancer cells adapt to severe tumor conditions and to discuss possible future research directions and therapeutic applications from the perspective of lipid metabolism.

2. Adaptive response mechanisms to glucose deprivation

Relationship to hypoxia. Generally, cancer cells adapt to hypoxia and glucose deficiency without relying on lipid metabolism, primarily through the hypoxia-inducible factor (HIF) pathway (11,12) and the unfolded protein response (UPR) (13) (Fig. 2). The UPR involves endoplasmic reticulum (ER)-associated degradation of incorrectly folded proteins produced under the above stress conditions, preventing accumulation of toxic misfolded proteins followed by ER stress. However, expression of HIF1α, required for adaptation to hypoxia, is impaired in cancer cells cultured under low-glucose conditions (14). The combination of hypoxia and glucose deficiency (HGD) is cytotoxic to cancer cells. Indeed, recent studies have shown that HGD induces cancer cell death in association with CRE-binding protein (15) and overproduction of poly (ADP-ribose) polymer (16). However, cancer cells can synergistically respond to HGD and activate genes required for adaptation to this harsh condition (17).

The common adaptive response mechanism in cancer cells exposed to HGD may involve both HIF pathway activation (18-20) and the UPR (13,15,16,19,20). Hypoxia induces the UPR through activation of the ER stress sensor molecules activating transcription factor 6, inositol-requiring protein 1 (IRE1), and PKR-like ER kinase (PERK) (1 in Fig. 2) (13,19), which helps cancer cells tolerate low-oxygen conditions. These mechanisms can be induced under hypoxia and/or glucose deficiency. The HIF pathway is mediated by hypoxia-inducible transcription factors HIF1α and HIF2α, which are mainly induced in mildly to moderately hypoxic tumor regions (Figs. 1 and 2), along with the constitutively expressed aryl hydrocarbon receptor nuclear translocator (ARNT) (2 in Fig. 2) (12).

Mammalian target of rapamycin (mTOR) plays a role in adaptation to HGD. mTOR complex 1 (mTORC1) promotes the translation of proteins, including HIFα proteins, to maintain energy homeostasis (3 in Fig. 2) (19,20). However, suppression of mTORC1 signaling can also be important for adapting to hypoxia by enabling appropriate mRNA translation and activating the UPR (19,20). mTOR can be inhibited through the HIF1α-REDD1 and HIF1α-BNIP3 pathways under hypoxia, suggesting a negative feedback loop between HIFα and mTOR (route 4 in Fig. 2) (19). Thus, HIFα, the UPR, and mTOR are interconnected under HGD (13,19).

Several studies have revealed the effects of HGD on cancer cell survival. Resistance to apoptosis induced under HGD is mediated by the serine/threonine kinase proviral integration site for Moloney murine leukemia virus 1 (PIM-1) in some cancer cells (21). Meanwhile, proline oxidase (POX) expression is increased under HGD in an AMP-activated protein kinase (AMPK)-dependent manner (22). Expression of both PIM-1 and POX is HIF-independent (5 in Fig. 2) (21,22). Survival of cancer cells exposed to HGD may be dependent on POX because proline oxidation results in ATP production under HGD (22). Thus, POX is a potential target of cancer therapy. HIF1α and the UPR cooperate to enhance the stemness of breast cancer cells via HIF1α binding to XBP1 under HGD (6 in Fig. 2) (23). HIF1α-driven expression of LIMS1 not only facilitates glucose uptake but also enhances HIF1α translation via the AKT-mTOR pathway in pancreatic cancer cells exposed to HGD (route 7 in Fig. 2), resulting in a cell survival advantage (24).

Recent studies have shown that GD generates an HGD-mimicking condition because even under normoxia,

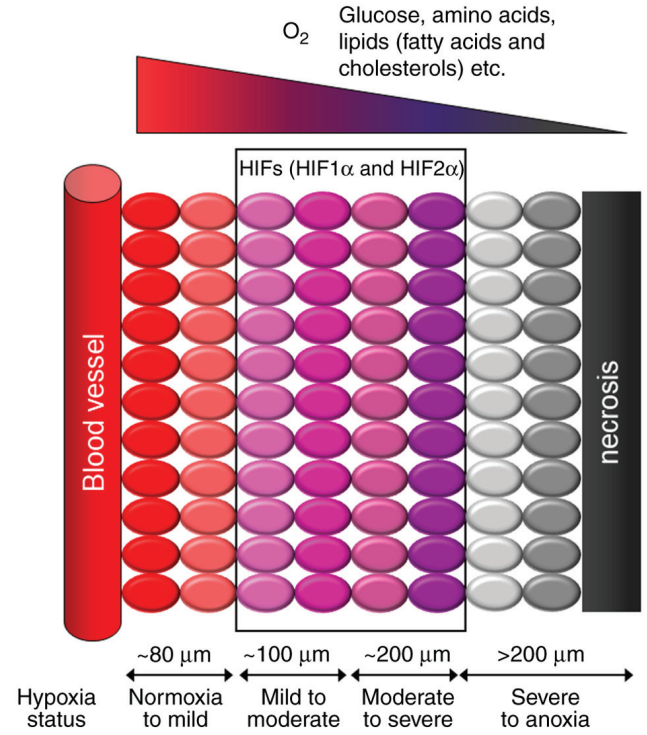

Figure 1. Gradient of blood component availability in tumor tissues based on distance from the bloodstream. Ovals of the same color represent cancer cell populations with identical hypoxia status. The necrosis area indicates regions where cancer cells are non-viable due to severe O_2 and nutrient deprivation. The tumor tissues within open rectangular area represents regions abundant in HIF. HIF, hypoxia-inducible factor.

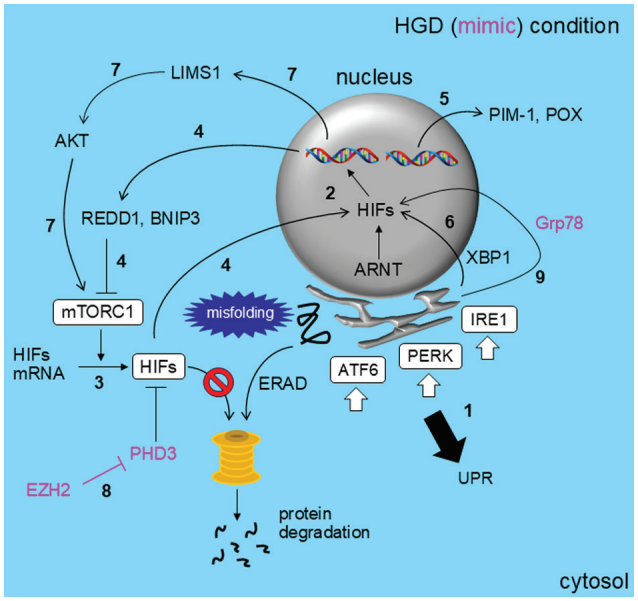

Figure 2. Relationship between HIFs and UPR under HGD. Cancer cells adapt to HGD stress through the UPR, mediated by (1) multiple ER stress sensor molecules and transcriptional activation driven by (2) the HIF-ARNT complex. HIF expression can be both activated and suppressed via (3,4) mTOR. This process is regulated through (7,8) the LIMS-Akt and EZH2-PDH3 pathways (5) HIF-independent transcriptional activation also contributes to adaptation under HGD. HIFs cooperate with (6) XBP1 and (9) Grp78 to activate downstream genes essential for the adaptive response. Molecules involved in HGD-mimicking conditions are shown in magenta. Arrows and T-bars indicate activating and suppressive processes, respectively. ERAD, ER-associated degradation.

expression of HIF1α can be induced by GD to augment cancer cell survival (25-27). This induction of HIF1α expression occurs through EZH2-dependent suppression of PHD3 expression (8 in Fig. 2) (25). This simple GD-driven pseudo-HGD condition with HIF1α expression through inhibition of its degradation augments the aggressiveness of lung adenocarcinoma cells (25). GD under normoxia also increases HIF1α expression via ER stress-inducible molecular chaperone GRP78 in pancreatic cancer cells to augment chemoresistance (9 in Fig. 2) (26). The GRP78-HIF1α complex binds to the regulatory region of the *HIF1A* gene to promote transcription. Thus, GRP78 can induce HIF1α expression at the mRNA level (26). In summary, GD can enhance tumor hypoxia by upregulating HIF1α expression at both the protein and mRNA levels. Meanwhile, lysophosphatidic acid receptors were shown to contribute to chemoresistance in pancreatic cancer cell line PANC-1 under HGD (28). Expression of immune checkpoint receptor PD-1 and TIGIT can be synergistically increased in esophageal cancer cells under HGD and is responsible for immune tolerance (29). The roles of HIFs and the UPR were not examined in these two studies (28,29).

Relationship to lipid metabolism. Glucose uptake and subsequent catabolism are activated in cancer cells. Recent studies have shown that GD influences lipid metabolism in cancer cells to support their survival, although its relationship to hypoxia has not yet been established. Indeed, some glioma cells have these characteristics and become susceptible to GD in culture (30). GD in cancer cells is associated with multiple lipid metabolism pathways, as summarized in Table I and Fig. 2. GD together with serum deficiency was also reported to drive the use of extracellular glutamine and lactate in glycerophospholipid synthesis for biomembrane generation via oxaloacetate-phosphoenolpyruvate conversion (Fig. 3A) in lung cancer cells (31). Mitochondrial phosphoenolpyruvate carboxykinase (PEPCK-M) plays key roles in this process (Fig. 3A) (31). Pharmacological activation of AMPK, a cellular energy sensor molecule, activates fatty acid oxidation (FAO) to acquire ATP in Akt-transformed cells under GD (30) (1 in Fig. 3B). Collectively, these studies have revealed novel mechanisms for cancer cell adaptation to severe nutrient deficiency.

Membrane phospholipids can be substrates for phospholipase D1-mediated autophagy in multiple cancer cell types under GD (32). FAs generated during this process (2 in Fig. 3B) can be used for FAO to sustain cell survival (32). In hepatocellular carcinoma and leukemia cells, GD activates MEK-ERK5 signaling to increase FA uptake (3 in Fig. 3B), followed by ATP generation through existing FAO activity (33). The importance of FAO under GD was also demonstrated in drug-resistant slow-cycling glioblastoma subpopulations (34). The same study showed that FA transport (4 in Fig. 3B) by fatty acid-binding protein (FABP)-7 is crucial for survival of mitochondria (oxidative phosphorylation)-active glioma cells (34). LD catabolism by lipophagy, followed by existing FAO activity (route 5 in Fig. 3B), also contributes to the survival of glucose-starved glioblastoma cells (35,36). This involves hyperactivation of mTOR (35) (Fig. 3B). Meanwhile, choline kinase 2 (CHKα2) is responsible for phosphorylation of LD-associated perilipins,

Table I. Reported relationships between glucose deprivation and lipid metabolism pathways associated with cancer progression.

Adaptive lipid metabolism	Key factor and mechanism responsible for adaptive lipid metabolism [reference]	Examined cancer cell (histological type) [reference]
FAO	AMPK activation (30), PLD1 (32), MEK5-ERK5 pathway activation (33), FABP7 (34), mTOR activation (35), lipophagy (35), CHKα2 (36), chaperone-mediated lipophagy (36), PIM1-GSK3β-PPARα pathway inactivation (37), PGM1 (38), FAS (38), CAF (42), oleic acid (42), autophagosome maturation (42), cancer stemness (42)	LN18, LN229 (brain) (30), MDA-MB-231 (breast) (32), MCF-7 (breast) (32), RCC4 (renal) (32), HCT116 (colon) (32), OCI-AML3 (lymphocyte) (33), BCL-P2 (lymphocyte) (33), HepG2 (liver) (33), HuH-7 (liver) (33), Primary cells (brain) (34), LN229 (brain) (35), GaMg (brain) (35), U87MG (brain) (35), A172 (brain) (35), HuH7 (liver) (36), U87 (brain) (36), GP06 (brain) (36), GP08 (brain) (36), PC3 (prostate) (37), PC3LN4 (prostate) (37), DU145 (prostate) (37), BGC-823 (gastric) (38), MKN-28 (gastric) (38), NCI-H460 (lung) (42)
Glycerophospholipid synthesis	PEPCK-M (31), glyceroneogenesis (31)	A549 (lung) (31), H23 (lung) (31)
Membrane lipid degradation	Autophagy (32), PLD1 (32)	MDA-MB-231 (32), MCF-7 (breast) (32), RCC4 (renal) (32), HCT116 (colon) (32)
FA transport	FABP7 (34)	Primary cells (brain) (34)
FA uptake	CD36 (33), LRP1 (33)	OCI-AML3 (lymphocyte) (33), BCL-P2 (lymphocyte) (33), HepG2 (liver) (33), HuH-7 (liver) (33)
LD catabolism	mTOR activation (35), lipophagy (35) CHKα2 (36), chaperone-mediated lipophagy (36), PIM1-GSK3β-PPARα pathway activation (37)	LN229 (brain) (35), GaMg (brain) (35), U87MG (brain) (35), A172 (brain) (35), HuH7 (liver) (36), U87 (brain) (36), GP06 (brain) (36), GP08 (brain) (36), PC3 (prostate) (37), PC3LN4 (prostate) (37), DU145 (prostate) (37)
Lipogenesis	PGM1 (38), glycogenolysis (38), FAS (38)	BGC-823 (gastric) (38), MKN-28 (gastric) (38)
Alteration of membrane lipid composition	Glycerophospholipids (31), phospholipids (phosphatidylethanolamine, cardiolipin, etc.) (39), cholesterol (39)	A549 (lung) (31), H23 (lung) (31), Caco-2 (colon) (39)
Prostaglandin E2 synthesis	UPR (41), AMPK activation (41), COX-2 (41)	HT29 (colon) (41), RG/C2 (colon) (41), AA/C1/SB/10C (colon) (41), SW480 (colon) (41)
Stearoyl-CoA desaturase expression	CAF (42), oleic acid supply (42), autophagy activation (42), F-actin polymerization-YAP nuclear translocation pathway (42), cancer stemness (42)	NCI-H460 (lung) (42)

AMPK, AMP-activated protein kinase; PLD1, phospholipase D1; PIM1, proviral integration site for Moloney murine leukemia virus 1; GSK3β, glycogen synthase kinase 3β; PPARα, peroxisome proliferator-activated receptor α; PEPCK-M, phosphoenolpyruvate carboxykinase-M; FABP7, fatty acid binding protein 7; CD36, cluster of differentiation 36; LRP1, lipoprotein receptor-related protein 1; CHKα2, choline kinase α2; PGM1, phosphoglucomutase 1; FAS, fatty acid synthase; UPR, unfolded protein response; COX-2, cyclooxygenase-2; CAF, cancer-associated fibroblast.

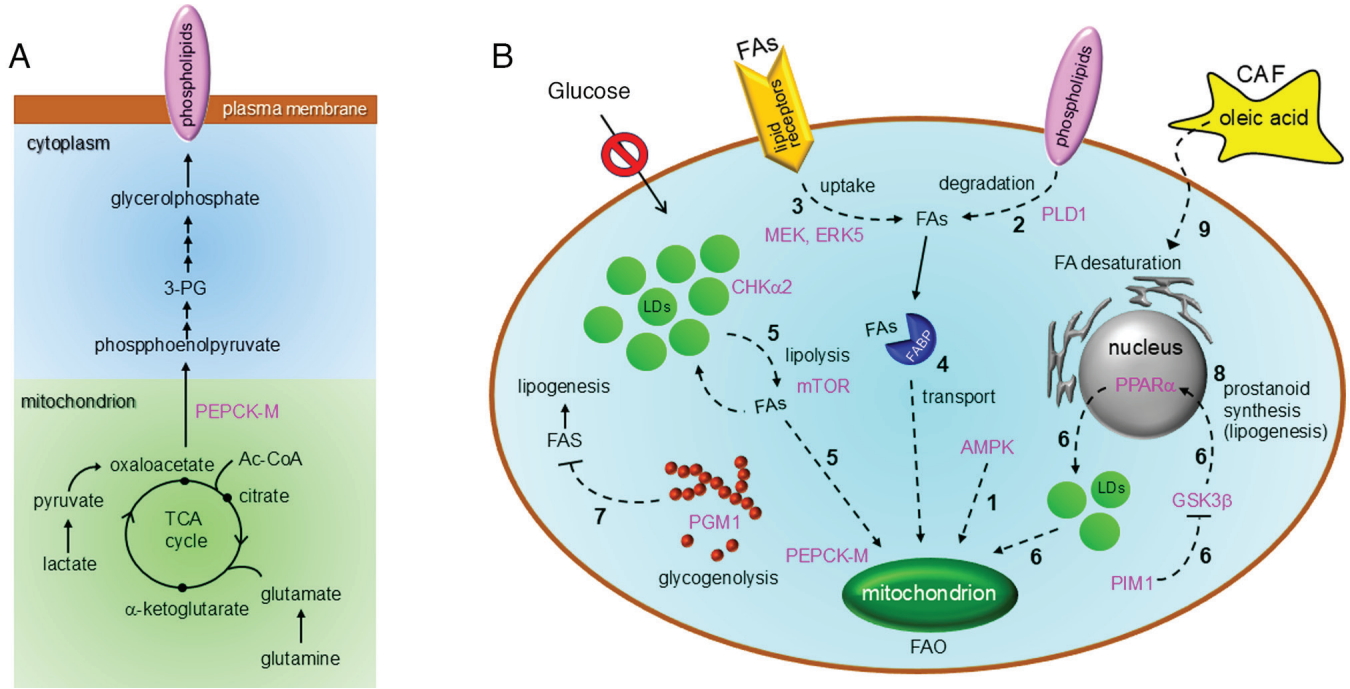

Figure 3. Localization of lipid metabolism pathways affected by GD (stop symbol) in cancer cells. Cancer cells adapt to GD through various lipid metabolism pathways. (A) Phospholipids can be synthesized *de novo* from glutamine and lactate in mitochondria under GD. The metabolic enzyme PEPCK-M plays a crucial role in this process by producing phosphoenolpyruvate via the TCA cycle. (B) AMPK can activate FAO (1). FAs generated through phospholipid lipolysis (2), LD breakdown (5,6), or uptake from the extracellular space (3) serve as energy sources via the FABP-FAO pathway (4). Lipogenesis mediated by FAS can be suppressed through glycogen digestion (7), while prostanoid synthesis may be activated (8). Exogenous monounsaturated FAs can enhance FA desaturation (9). The subcellular localizations of FA desaturation (cytoplasm, ER) are based on data from the Human Protein Atlas (https://www.proteinatlas.org), while the nuclear membrane localization of prostanoid synthesis is based on the information from a previous study (40). Dotted arrows and T-bars with numbers represent active processes in response to GD. Cellular events and biomolecules involved are shown in black, while enzymes and molecules critical for metabolic processes are highlighted in magenta. See the text for further details on these processes.

finally resulting in chaperone-mediated autophagy-driven degradation of LDs to generate FAs (35) (route 5 in Fig. 3B). FAO under GD is also important for prostate cancer cells, in which LD accumulation via the PIM1-GSK3β-PPARα axis can be activated under nutrient stress conditions for FA generation (37) (route 6 in Fig. 3B).

Glycogenolysis serves as an alternative pathway for cellular glucose supply under GD. Phosphoglucomutase PGM1, a key enzyme for glycogenolysis followed by glycolysis, contributes to the viability of gastric cancer cells exposed to GD by suppressing lipogenesis (38) (7 in Fig. 3B). FAS can compensate for the reduced cell viability caused by PGM1 inhibition under GD conditions (38). Thus, combined inhibition of interconversion of the phosphate position within glucose molecules and FAS may be promising for gastric cancer treatment (38). A study using colon cancer cell line Caco-2 revealed that the composition of phospholipids, cholesterol, and unsaturated FAs in the cell membrane is considerably altered under GD, leading to metabolic adaptations that augment cell survival (39). GD also increases prostaglandin E2 synthesis at the nuclear membrane (40) (8 in Fig. 3B) by repressing 15-hydroxyprostaglandin dehydrogenase expression in colon cancer cells, resulting in a survival advantage for these cells (41). The stemness of lung cancer cells exposed to GD may be enhanced by oleic acid supplied by surrounding cancer-associated fibroblasts (CAFs), followed by stearoyl-CoA desaturase expression (9 in Fig. 3B), nuclear translocation of polymerized actin, and yes-associated protein (42). This process can be inhibited by treatment with an FAO inhibitor (42).

In summary, this section has revealed that various cancer cells generally circumvent GD through FAO (Table I). Additionally, the biosynthesis of glycerophospholipids and prostaglandins can contribute to their adaption to GD.

3. Adaptive response mechanisms to amino acid deprivation through lipid metabolism and their correlation with hypoxia

In addition to their role as protein components, AAs, such as glucose, can serve as major energy sources. Numerous studies have demonstrated the effects of AA deficiencies on cancer phenotypes, similar to those observed in GD. However, there is limited knowledge on their correlations with hypoxia and lipid metabolism. This section will primarily address this issue. Studies have generally demonstrated that AA deficiencies are associated with multiple lipid metabolism pathways (Table II) and hypoxia in cancer cells.

Glutamine deprivation. Glutamine is another primary nutrient for cancer cells in addition to glucose. The levels of non-essential AAs, including glutamine, in pancreatic cancer tissues are considerably lower than those in adjacent benign tissues (43). In cells with an inactivated von Hippel Lindau (*VHL*) gene under hypoxia, glutamine is used to generate α-ketoglutarate, which is then used to produce the citrate required for *de novo* LCFA synthesis through reductive carboxylation (44,45) (route 1 in Fig. 4A) and the glutathione (GSH) synthesis

Table II. Reported relationships between amino acid deficiencies and lipid metabolism pathways in cancer cells.

Deprived amino acid	Responsive lipid metabolism	Key factor and mechanism responsible for adaptive lipid metabolism [reference]	Examined cancer cell line (histological type) [reference]
Glutamine	Suppression of lipogenesis	Loss of reductive carboxylation[a] (44), LD-lipophagy, followed by suppression of cholesterol synthesis (53)	PRC3 (kidney) (44), 786-O (kidney) (44), UMRC2 (kidney) (44), HepG2 (liver) (53), HuH6 (liver) (53), Huh7 (liver) (53)
	LPO	Impairment of glutathione synthesis[a] (46), ferroptosis[a] (46)	RCC-4 (kidney) (46), 786-O (kidney) (46)
	FAO activation	Sestrin2-mTORCs pathway activation (47), CHTM1 (48), HRD1 (51), CPT2 degradation (51), PI3K-C2γ pathway inactivation (52), glutamine auxotroph (52), AMPK-CHKα2-LD-ATGL pathway activation (50)	H358 (lung) (47), H1299 (lung) (47), H460 (Lung) (47), MCF-7 (breast) (48), RKO (colon) (48), UACC-62 (skin) (48), MDA-MB-231 (breast) (51), Capan1 (pancreas) (52), MiaPaca2 (pancreas) (52), Panc1 (pancreas) (52), H322 (lung) (50), H358 (lung) (50)
	Lipogenesis	CHTM1 (48), PKC-CREB-PGC-1α pathway activation (48), SREBP1-ACC1-LD pathway pathway activation (49), SREBP1-glutamine synthesis activation (49),	MCF-7 (breast) (48), RKO (colon) (48), UACC-62 (skin) (48), HepG2 (liver) (49)
	Lipolysis	AMPK-CHKα2-LD-ATGL pathway activation (50)	H322 (lung) (50), H358 (lung) (50)
	Maintenance of cellular lipid balance	TRIAP-1-p53 interaction (54), phospholipids and sterols homeostasis (54)	HCT-116 (colon) (54)
Serine (Glycine)	LPO inhibition	Glutathione synthesis (59), p53-p21 pathway activation (59)	HCT116 (colon) (59), RKO (colon) (59)
	FAO activation	Pyruvate transfer to the TCA cycle (59)	HCT116 (colon) (59), RKO (colon) (59)
	FAO suppression	Impairment of ceramide synthesis[a] (58), mitochondrial dysfunction[a] (58)	HCT116 (colon) (58), HT29 (colon) (58)
	Deoxyceramide synthesis	Serine to alanine substitution within ceramide molecule[a] (60, 61)	HCT116 (colon) (60, 61), MOLT-4 (lymphocyte) (61), HEK293T (kidney) (61)
	Accumulation of cellular sphingosine	SK1 degradation (61), autonomous serine synthesis (61)	HCT116 (colon) (61), MOLT-4 (lymphocyte) (61), HEK293T (kidney) (61)
Cysteine	Suppression of per-oxidized lipid accumulation	Activation of FA metabolism (64), GPX4 expression (64), glutathione synthesis (67,68), NRF2-CBS pathway (67), macropinocytosis of albumin (68), iron storage (68, 69), ATM-MTF1-ferritin/FPN1 pathway (69), CISD3 (70), glutaminolysis (70), conversion of peroxidized lipid to lipid alcohol (71), anti-oxidant tryptophan metabolites (71)	HL60 (bone marrow) (64), MOLM13 (bone marrow) (64), SKOV3 (ovary) (67), OVCA429 (ovary) (67), HT-1080 (fibroblast) (68,69), A375 (skin) (68), T98G (brain) (68), U2OS (bone) (68), PaTu8988T (pancreas) (68), GS187 (brain) (68), MDA-MB-231 (breast) (69), RCC4 (kidney) (69), HEK293T (kidney) (69), HL60 (bone marrow) (70), 786-O (kidney) (71), AsPC-1 (pancreas) (71), CFPAC-1 (pancreas) (71), PANC-1 (pancreas) (71), U251 (brain) (71), Be2C, (neuroblast) (71)
	Lipid peroxidation	Suppression of glutathione synthesis[a] (46,64), ferroptosis[a] (46,64)	RCC-4 (kidney) (46), 786-O (kidney) (46), HL60 (bone marrow) (64), MOLM13 (bone marrow) (64)

Table II. Continued.

Deprived amino acid	Responsive lipid metabolism	Key factor and mechanism responsible for adaptive lipid metabolism [reference]	Examined cancer cell line (histological type) [reference]
Arginine	Suppression of FAO	Arginine auxotroph (73), impairment of mitochondria function[a] (73), cytotoxic autophagy[a] (73) LD accumulation (73)	MDA-MB-231 (breast) (73), T47-D (breast) (73)
	Lipid peroxidation	Arginine auxotroph (74), inhibition of mTOR-SREBP1-SCD5 pathway[a] (74), ferroptosis[a] (74)	H1299 (lung) (74), HCC827 (lung) (74)
	Suppression of lipogenesis	Arginine auxotroph (75,76), activation of MEK-ERK-cMyc-ASS1 pathway (75), reduction of ACLY (76), ACC1 (76), and FAS (76) synthesis	SKLMS-1 (vulva) (75), A2058 (skin) (76), SK-Mel-2 (skin) (76)
Methionine	Phospholipid metabolism	Increase of cellular glycerophospholipids (78,79). Decrease of choline (78) and phosphatidylcholine (79).	B16 (mouse skin) (78), HepG2 (liver) (79)
	Impairment of cholesterol biosynthesis, facilitation of cholesterol excretion	Suppression of SREBP2-FOXM1 axis[a] (80), inhibition of S-adenosylmethionine synthesis[a] (80)	In-house human glioma initiating cell lines (brain) (80)
	Lipid peroxidation	Suppression of glutathione synthesis[a] (65), ferroptosis[a] (65)	MG1-4 (mouse brain) (65), TS543 (brain) (65), KNS42 (brain) (65)

[a]Toxic events for cancer progression. LPO, lipid peroxidation; CHTM1, coiled-coil helix tumor and metabolism 1; HRD1, HMG-CoA reductase degradation protein 1; CPT2, carnitine palmitoyltransferase 2; PI3K-C2γ, phosphoinositide 3-kinase-C2γ; PKC, protein kinase C; CREB, CRE-binding protein; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; SREBP1, sterol regulatory element binding protein-1; ACC1, acetyl-CoA carboxylase 1; AMPK, AMP-activated protein kinase; CHKα2, choline kinase α2; ATGL, adipose triglyceride lipase; TRIAP-1, TP53-regulated inhibitor of apoptosis 1; SK1, sphingosine kinase 1; GPX4, glutathione peroxidase 4; NRF2, nuclear factor-erythroid 2-related factor-2; CBS, cystathionine β-synthase; ATM, ataxia-telangiectasia mutated; MTF1, metal regulatory transcription factor 1; FPN1, ferroportin; CISD3, CDGSH iron sulfur domain 3; SCD5, stearoyl-CoA desaturase 5; c-Myc, MYC proto-oncogene, bHLH transcription factor; ASS1, argininosuccinate synthetase 1; ACLY, ATP citrate lyase; FAS, fatty acid synthase; SREBP2, sterol regulatory element binding protein 2; FOXM1, forkhead box M1.

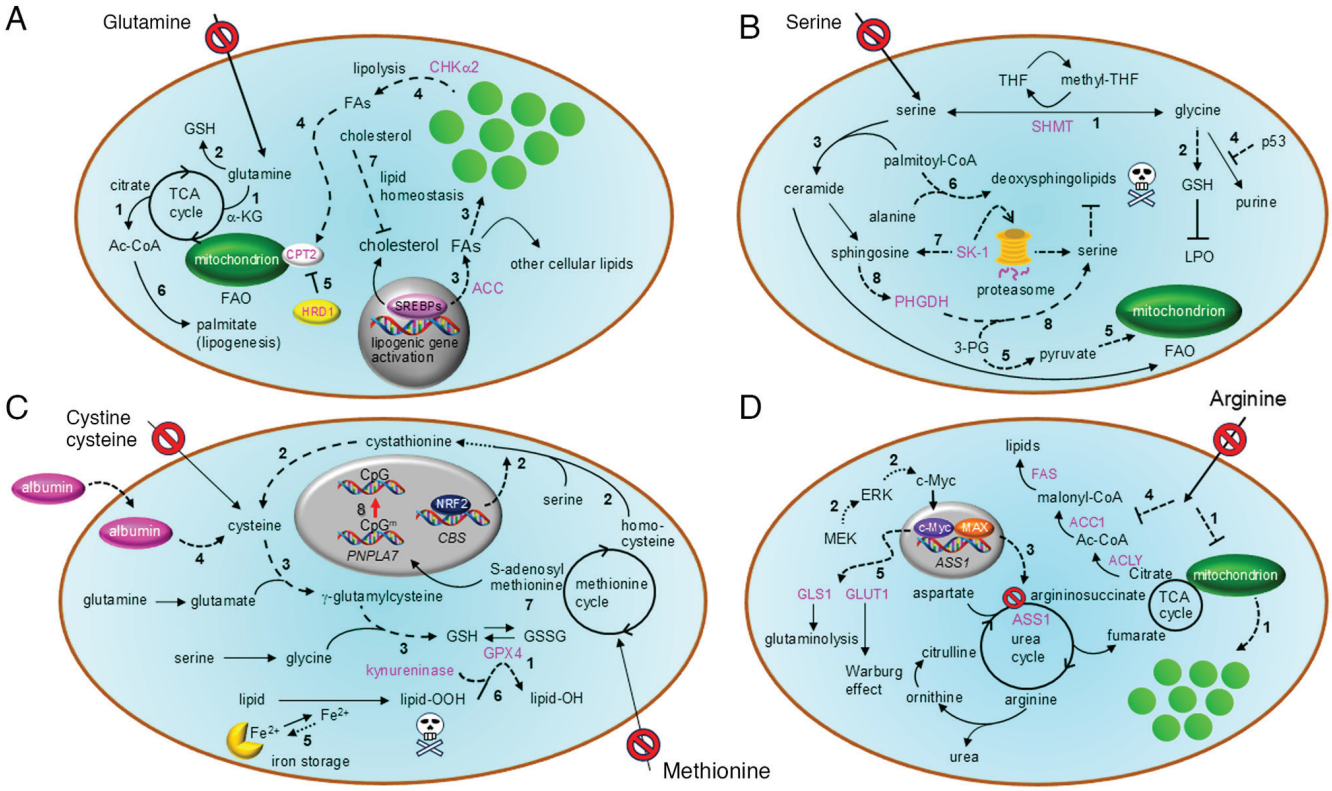

Figure 4. Localization of metabolic networks in cancer cells affected by (A) GlnD, (B) SD, (C) CD and MD, and (D) AD. (A) GlnD induces both anabolism and catabolism of LD. FAs generated through lipolysis can serve as energy sources. Cellular cholesterol levels may be suppressed in response to GlnD to maintain lipid homeostasis. (B) SD induces GSH synthesis from glycine while suppressing purine synthesis via p53. Toxic deoxysphingolipids may be produced under SD, but this toxicity can be mitigated by autonomously synthesized serine, associated with elevated PHGDH expression. 3-PG generated during this process can serve as an energy source via FAO. (C) CD activates anti-ferroptosis mechanisms by promoting GSH synthesis and inhibiting the accumulation of toxic peroxidized lipids. MD induces gene demethylation and contributes to resistance to MD stress through glycerophospholipid synthesis. (D) AD promotes autonomous arginine synthesis through overexpression of the ASS1 gene. This adaptation mechanism involves inhibition of lipogenesis and activation of glycolysis and glutaminolysis, rather than FAO. Arrows and T-bars represent activating and suppressive processes, respectively. Dotted symbols with numbers designate active processes in response to AA deficiency (stop symbols). See the text for additional details. Metabolic enzymes are highlighted in magenta.

(2 in Fig. 4A) necessary for suppression of lipid peroxide accumulation, which is responsible for ferroptosis (46). Thus, clear cell renal cell carcinoma (ccRCC) cells lacking functional *VHL* are susceptible to glutamine deficiency (GlnD) caused by glutaminase inhibition (44) or glutamine withdrawal from the culture medium (45) (Table II).

Cancer cells can adapt to stressful GlnD conditions through multiple metabolic mechanisms. A recent study using lung cancer cell lines showed that differential regulation of mTORC1 and mTORC2 via Sestrin2, followed by FAO, contributes to cell survival under GlnD (47) (Table II). Under both GD and GlnD, mitochondrial protein coiled-coil helix tumor and metabolism 1 can facilitate LCFA synthesis and FAO via LD formation in multiple cancer cells (48) (routes 3 and 4 in Fig. 4A and Table II). GlnD likely activates the *SREBF1* gene, which encodes the lipogenic enzyme SREBP1 (49). SREBF1 activation, mediated by O-linked N-acetylglucosaminylated transcription factor specificity protein 1 (Sp1) and followed by acetyl-CoA carboxylase (ACC) expression, contributes to LD biosynthesis in various cancer cells (49) (route 3 in Fig. 4A). Similar to the previously described glioblastoma cell response to GD (35), CHKα2 plays a key role in LD lipolysis in lung cancer cells exposed to GlnD (50) (route 4 in Fig. 4A and Table II). In this context, neutral lipolysis and lipophagy likely contribute to LD catabolism (route 4 in Fig. 4A). Notably, the same study demonstrated that phosphorylation of CHKα2 at S279, which is involved in neutral lipolysis, is associated with a worse prognosis in patients with non-small-cell lung cancer (50).

HMG-CoA reductase degradation protein 1 (HRD1) was found to suppress the proliferation of breast cancer cell line MDA-MB-231 through inhibition of FAO (51). HRD1 can interact and ubiquitinate FA transporter protein carnitine palmitoyltransferase 2 (CPT2) (5 in Fig. 4A), resulting in blockade of mitochondrial LCFA transport through its degradation (51). Under GlnD, this mechanism can be abolished to activate FAO, resulting in resistance to glutaminase inhibitors. Thus, simultaneous inhibition of FAO and glutamate production may be therapeutically promising, and high HRD1 expression potentially predicts better efficacy of glutaminase inhibitors (51).

PI3K-C2γ expression is inactivated to activate mTOR in cancer cells from pancreatic tumor tissues. These cells depend on exogenous glutamine to activate lipogenesis (52) (6 in Fig. 4A). Thus, treatment with mTOR and glutaminase inhibitors may be therapeutically beneficial. GlnD induces lipophagy-driven LD degradation to increase cellular cholesterol levels in hepatocellular carcinoma cells (53) (7 in Fig. 4A). Cholesterol inhibits SREBP2 maturation, leading to decreased cholesterol synthesis, which helps maintain redox

balance and provides a survival advantage to cancer cells under GlnD conditions (53). Interaction between p53 and TP53-regulated inhibitor of apoptosis 1 (TRIAP1) may also be important for survival of colon cancer cells under GlnD (54) (Table II). TRIAP1 affects lipid homeostasis through multiple lipids, including glycerolipids, sphingolipids, and cholesterols, in HCT116 cells (Table II). The TRIAP1-p53 interaction is important for glutamine metabolism. Indeed, under GlnD, p53 can compensate for TRIAP1 function to overcome metabolic stress (54). Collectively, GlnD can couple to multiple lipid metabolism pathways (Table II). Cancer cells likely acquire ATP through the activation of FAO via LD metabolism under this nutrient stress (Fig. 4A). Maintaining cellular lipid homeostasis is also important (Fig. 4A).

GlnD associated with hypoxia is known to trigger expression of UPR-executor transcription factor ATF4 (19,20) in glioblastoma cells (55). This UPR-mediated stress response is responsible for resistance to temozolomide treatment (55). Hypoxia with GlnD can also promote cancer progression through epigenetic mechanisms. In melanoma tissue, the glutamine concentration in the hypoxic tumor core region is considerably lower than that in the tumor periphery (56). Hypoxia with GlnD can cause hypermethylation of histones through inhibition of demethylation and promote cancer cell dedifferentiation, resulting in resistance to BRAF inhibitor treatment (56). The implications for lipid metabolism involvement in these hypoxia- and GlnD-associated features observed in tumor tissues remain to be determined.

Serine and glycine deprivation. Serine and glycine can be enzymatically interconverted through a single reaction mediated by serine hydroxymethyltransferase, involving the conversion of tetrahydrofolate to its methylated form (1 in Fig. 4B), and they contribute to common metabolic pathways such as GSH synthesis (57,58) (2 in Fig. 4B). Thus, studies have tended to consider the effects of these AAs together (Fig. 4B, Table II).

Studies using colon cancer cell line HCT116 showed that serine/glycine deficiency (SGD) can suppress FAO through impaired mitochondrial function (58). Specifically, the ceramide level is decreased in serine-depleted cells (3 in Fig. 4B), leading to mitochondrial dysfunction (58). Thus, restriction of the serine supply is promising in treatment of p53-deficient cancers. However, SGD causes metabolic reprogramming with increased oxidative phosphorylation activity (59). p53-dependent synthesis of GSH with suppression of purine synthesis (4 in Fig. 4B), followed by scavenging of reactive oxygen species, can contribute to resistance of cancer cells against this metabolic stress (59). This process is accompanied by an increase in pyruvate transfer via 3-phosphoglycerate (3-PG) to the mitochondria, which activates FAO (route 5 in Fig. 4B). Furthermore, SGD facilitates the biosynthesis of toxic deoxysphingolipid, in which serine residues are substituted with alanine residues (6 in Fig. 4B), in cancer cells (60). Thus, dietary restriction and pharmacological targeting of the serine supply pathway can lead to tumor regression. This effect was prominent for growth of alanine-rich spheroid cancer cells (60). A more recent study further demonstrated that deoxysphingolipid (deoxysphinganine) generation is non-toxic and important for adaptation of cancer cells to SGD (61). This response mechanism involves accumulation of sphingosine in cancer cells due to the proteasomal degradation of sphingosine kinase 1 (7 in Fig. 4B), leading to increased expression of phosphoglycerate dehydrogenase (PHGDH) and subsequent *de novo* serine synthesis (route 8 in Fig. 4B) to overcome SGD (61). In summary, cancer cells can adapt to serine deficiency through inhibition of lipid peroxidation, activation of FAO, and modulation of sphingolipid biosynthesis.

Regarding the relationship between SGD and hypoxia, glioblastoma cells were reported to activate the AMPK-HIF1α pathway and induce a pseudo-hypoxia condition under SGD to bypass this metabolic stress (62). The effects of lipid metabolism involvement in this adaptation mechanism remain to be elucidated.

Cysteine deprivation. The major source of cellular cysteine is dietary cystine, which is metabolically associated with glutamine (63). Cysteine is also produced by *de novo* synthesis from methionine (63). The major effect of cysteine deficiency (CD) on cancer cells is impaired GSH synthesis, resulting in ferroptosis through accumulation of toxic peroxidized phospholipids (Fig. 4C, Table II) (46,64). Thus, CD may be therapeutically beneficial (46,64-66).

The mechanisms underlying how cancer cells circumvent CD fall into a single category (Table II): ferroptosis resistance through suppression of peroxidized lipid accumulation. Multiple pathways may be involved in this process in various cancer cells (Table II). For example, acute myeloid leukemia cells are auxotrophic for cysteine and can acquire CD resistance through overexpression of glutathione peroxidase 4 (1 in Fig. 4C) and microsomal glutathione-S-transferase 1, which may be associated with activation of FA metabolism (64) (Table II). In *VHL*-defective ccRCC cells, generation of peroxidized lipids is suppressed by FAO inhibition and GSH synthesis (46). In ovarian cancer cells, transcription factor NRF2 enhances cystathionine β-synthase (*CBS*) gene expression and activates autonomous synthesis of cysteine (route 2 in Fig. 4C), resulting in resistance to CD-induced ferroptosis through GSH synthesis (route 3 in Fig. 4C) (67). A recent study showed that albumin can be an extracellular source of cysteine under CD (68). Albumin incorporated into cancer cells via macro-pinocytosis in association with mTOR inhibition undergoes lysosomal degradation (68). Cysteine released into the cytoplasm also contributes to GSH synthesis (4 and route 3 in Fig. 4C), thereby preventing ferroptosis of cancer cells (68). This mechanism is especially important under spheroid culture conditions associated with tumor-like stress conditions (68).

Deprivation of cellular free iron ions is an alternative mechanism of ferroptosis resistance. Expression of genes involved in cellular iron storage can be increased via the ATM-MTF1 axis under CD. As a result, the balance between iron storage and release is expected to shift toward storage (5 in Fig. 4C), leading to ferroptosis resistance in multiple cancer cells (69). Expression of iron-sulfur cluster protein CISD3 is also increased in cancer cells and contributes to iron storage under CD, followed by ferroptosis resistance (70).

Tryptophane metabolites contribute to ferroptosis resistance under CD through a detoxification mechanism. Specifically,

Table III. Reported effects of hypoxia and lipid starvation on cancer cell response.

Deprived lipids	Related cellular events [reference]	Examined cancer cells (histological origin) [reference]
Exogenous FA	ER expansion[a] (81), UPR-induced cell death[a] (81)	MCF7 (breast) (81), RCC10 (kidney) (81), U251 (brain) (81), RT4 (bladder) (81), A498 (kidney) (81)
	UPR (93), ICAM-1-driven resistance to apoptosis (95)	OVSAYO (ovary) (93,95), OVISE (ovary) (93,95)
	Neutral lipase-mediated LD catabolism (88), oleate-mediated suppression of lipotoxicity (88)	A498 (kidney) (88)
	Lipophagy-mediated LD catabolism (98)	OVSAYO (ovary) (98), OVISE (ovary) (98)
	EMT (96)	OVSAYO (ovary) (96), OVISE (ovary) (96)
Endogenous FA	Impairment of NAD^+ production[a] (82), induction of lipid auxotroph through inhibition of lipogenesis (82)	Hela (uterus) (82)
Cholesterol	Secretion of procoagulant extracellular vesicles (99)	OVSAYO (ovary) (99), OVISE (ovary) (99)
	SREBP1-driven lipogenic gene expression (100), apoptosis (100), impairment of spheroid growth (100)	U87 (brain) (100), U251 (brain) (100)
	SREBP2-driven *ACSS2* gene expression (101), palmitate synthesis (101), phospholipid synthesis (101)	BT474 (breast) (101), DU145 (prostate) (101)

[a]Toxic events for cancer progression. ER, endoplasmic reticulum; FA, fatty acid; UPR, unfolded protein response; ICAM-1, intercellular adhesion molecule-1; LD, lipid droplet; EMT, epithelial-mesenchymal transition; NAD, nicotinamide adenine dinucleotide; SREBP, sterol regulatory element binding protein.

serotonin and 3-hydroxy-anthranilic acid produced by kynureninase act as radical trapping agents and reduce peroxidized lipids to non-toxic lipid alcohols (71) (6 in Fig. 4C). Overall, cancer cells utilize multiple molecular defense mechanisms against CD-driven ferroptosis (Table II).

In the context of CD and hypoxia, CD-induced death of MDA-MB-231 cells can be alleviated by hypoxia through inhibition of ATF4 expression (72). Thus, hypoxia may reduce CD-mediated cytotoxicity in certain cancer cells.

Arginine deprivation. Cancer cells are also sensitive to arginine deficiency (AD), and this vulnerability is often associated with lipid metabolism (Table II). Expression of argininosuccinate synthetase 1 (ASS1), an enzyme in the urea cycle (Fig. 4D) that also catalyzes arginine biosynthesis, is low in >60% of clinical breast cancer samples (73). Thus, many cancer cells are arginine auxotrophs (Table II). AD induces cytotoxic autophagy in breast cancer cells, leading to cell death due to impaired mitochondrial function (Table II). In such cases, FAO suppression is followed by a metabolic shift to increase LDs (73) (route 1 in Fig. 4D). Meanwhile, ASS1-high non-small-cell lung cancer cells can confer ferroptosis resistance through monounsaturated FA synthesis. To facilitate this process, ASS1-driven synthesis of arginine activates the mTOR-SREBP1-SCD5 pathway to cause unsaturation of autonomously synthesized FAs, leading to inhibition of peroxidized lipid generation (74). This mechanism provides additional insight into why arginine auxotroph lung cancer cells are susceptible to AD-induced cell death. These observations suggest that arginine-deficient diets may be a therapeutic strategy through induction of ferroptosis. However, cancer cells can circumvent this stress condition. For example, AD can activate the MEK-ERK signaling pathway (route 2 in Fig. 4D) to induce c-Myc-Max transcription factor-driven *ASS1* gene activation (3 in Fig. 4D) in ASS1-negative vulvar leiomyosarcoma (SKLMS-1) cells (75) (Table II). This cellular response causes adaptive metabolic reprogramming, including reduced ACLY expression, followed by suppression of *de novo* FA synthesis (75) (4 in Fig. 4D). Moreover, reports have described resistance to pharmacological AD in melanoma cells with ASS1 overexpression. In these cells, *de novo* lipogenesis is also inhibited through suppression of ACLY (Fig. 4D), acetyl-CoA carboxylase 1 (ACC1 in Fig. 4D), and FAS (Fig. 4D) to promote the Warburg effect (76). In this scenario, c-Myc contributes to AD resistance not only through ASS1 expression but also by enhancing glycolysis and glutaminolysis (5 in Fig. 4D) via the expression of glucose transporter 1 and glutaminase, respectively. Collectively, cancer cells can evade the effects of AD by autonomously synthesizing arginine, with the Warburg effect, rather than FAO, likely playing a key role in supporting cell survival under AD.

Under hypoxia, pharmacological AD inhibits expression of HIFs, inducible nitric oxide synthase, and ASS1 in HCT116 cells to inhibit tumor growth (77). This effect is associated with UPR induction. ASS1-deficient bladder cancer cell line UMUC3 shows greater sensitivity to hypoxia under AD (77). Thus, hypoxic cancer cells are vulnerable to AD.

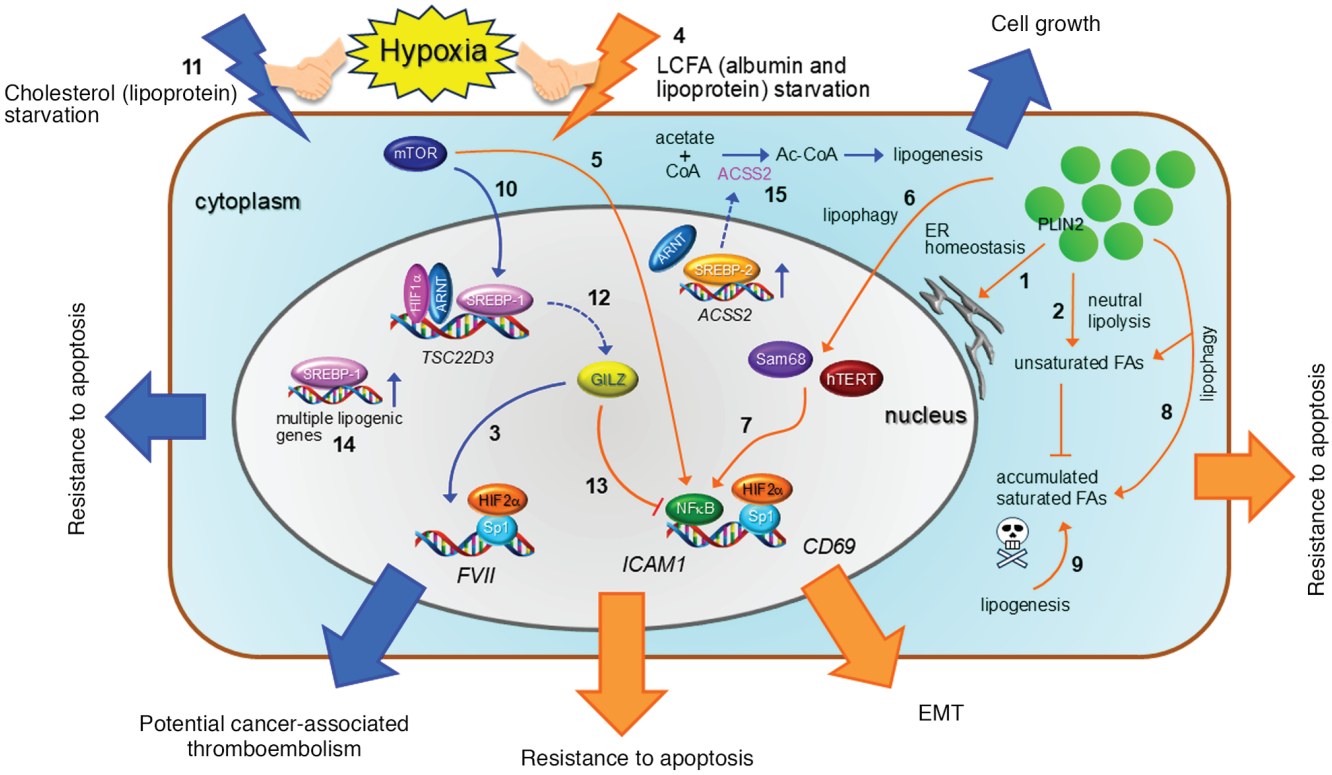

Figure 5. Overview of lipid starvation and hypoxia-driven cancer cell phenotypes. Cancer cells adapt to lipid (LCFA and cholesterol) deprivation and hypoxia through various resistance mechanisms. These malignant phenotypes are mediated by lipolysis and lipogenesis. Transcription factors such as HIFs, ARNT, SREBPs, NFκB, and Sp1, along with cofactors like GILZ, Sam68, and hTERT, play key roles in these processes. Handshake symbols between hypoxia and orange or blue lightning symbols represent LCFA starvation + hypoxia and cholesterol starvation + hypoxia, respectively. Plain arrows, dashed arrows, and T-bars indicate activation processes, protein expression, and inhibition processes, respectively. See the text for further details on the numbered items. Orange and blue symbols correspond to processes induced by LCFA and cholesterol starvation, respectively. Bold orange and blue arrows represent phenotype expressions resulting from LCFA and cholesterol starvation, respectively. EMT, epithelial-mesenchymal transition; PLIN2, perilipin 2.

Methionine deprivation. Deprivation of methionine, an essential AA, from culture medium likely affects lipid metabolism in cancer cells (Fig. 4C, Table II). Methionine deprivation (MD) is linked to GSH synthesis through the methionine cycle and cysteine synthesis pathway (routes 2 and 3 in Fig. 4C). Consequently, MD can impair GSH synthesis (65), leading to ferroptosis, similar to the effect of CD. However, acute myeloid leukemia cells are cysteine auxotrophs as indicated by the fact that methionine supplementation does not rescue them from CD-driven ferroptosis (64). MD also affects cellular lipids by increasing phosphorylethanolamine and decreasing choline (Table II), thereby contributing to a synergistic therapeutic effect with chloroethylnitrosourea treatment (78). Meanwhile, methionine is a precursor of S-adenosylmethionine (7 in Fig. 4C), a key methyl donor for biomolecules. Thus, MD affects methylation-driven lipid metabolism pathways. For example, MD causes S-adenosylmethionine deficiency in HepG2 cells and enhances glycerophosphocholine synthesis through demethylation of CpGs within the *PNPLA7* promoter region (79) (8 in Fig. 4C). This adaptation mechanism potentially promotes cancer progression via activation of mitochondrial oxidative phosphorylation (79). MD may also be therapeutically promising for glioma-initiating cells because it impairs cholesterol synthesis and increases cholesterol excretion, thereby suppressing key glioma-initiating cell functions (80).

4. Adaptive response mechanisms to simultaneous deprivation of O_2 and lipids

Cancer cells can utilize FAs obtained through lipogenesis and uptake from extracellular spaces under glucose and AA deficiency. However, the exogenous supply of lipids is restricted in cancer cells within poorly vascularized tumor tissues. This section will discuss recently revealed adaptive response mechanisms to restricted supply of both lipids and molecular oxygen, although the observations are currently limited to certain cancer types.

Adaptive responses to LCFA starvation and hypoxia in cancer cells. In general, tumor tissues are poorly vascularized. Thus, many blood components, including lipids, are poorly supplied. Impairment of lipogenesis may also enhance lipid insufficiency in cancer cells exposed to hypoxia with limited exogenous lipid supply. The effect of simultaneous deprivation of lipids and molecular oxygen on cancer cells was first demonstrated by experiments examining how serum starvation and hypoxia (SSH) affects their phenotype in relation to mTOR activity (81). The same study using mouse embryonic fibroblast cells and various cancer cells, including kidney cancer cells, showed that mTOR activation under SSH augments ER stress, resulting in UPR-mediated cell death (Table III) (81). This is likely due to abnormal ER expansion induced by increased protein synthesis and insufficient unsaturated LCFA

supply because cell death was alleviated by supplementation of albumin-conjugated oleic acid (81).

Hypoxia and delipidated serum cell culture conditions, characterized by poor supply of molecular oxygen as an electron acceptor and poor supply of extracellular lipids, was also shown to reduce regeneration of NAD^+, a cofactor required for lipogenic citrate production in cancer cells, followed by cell proliferation (82). Thus, cancer cells exposed to SSH are likely to become lipid auxotrophs (Table III). However, NAD^+-independent metabolism of exogenous acetate to acetyl-CoA followed by lipogenesis in cancer cells can rescue this auxotrophy (82).

ccRCC is a histological subtype of most kidney cancers (70-80%). Most of these cancer cells lack VHL function, resulting in constitutive HIF expression. Consequently, these cancer cells exhibit hypoxia-mimicking phenotypes (83,84). The phenotypes of ccRCC cells, such as ER homeostasis (83), motility (85), invasiveness (85), and anti-apoptosis (84), are highly dependent on LD biogenesis rather than LD catabolism (83-85). The kidney is a well-perfused organ (85), and studies on this cancer type under true hypoxic conditions are limited because ccRCC cells express HIF even in normoxic environments. However, hypoxia is a general tumor condition. Indeed, hypoxic regions exist within the normal renal medulla (86) and renal tumors (87), and adaptation of cancer cells to SSH may contribute to kidney cancer progression (Table III).

The HIF2α-perilipin 2 pathway contributes to ER homeostasis-mediated survival of ccRCC cells under SSH (1 in Fig. 5 and Table III) (83). LD catabolism also contributes to ccRCC cell phenotypes under LCFA starvation and hypoxia. LDs in cancer cells undergo hormone-sensitive lipase-driven degradation under SSH to maintain the cellular unsaturated FA (oleic acid) level, thereby suppressing the effect of toxic saturated FAs synthesized under hypoxia (2 in Fig. 5 and Table III) (88). Thus, the roles of LDs in malignancy are context-dependent.

Ovarian clear cell carcinoma (OCCC) has morphological and biological similarities to ccRCC (89). As described above, ccRCC cells exhibit hypoxia-mimicking phenotypes. This characteristic may also be true for OCCC cells because the HIF pathway is more active in this cancer subtype than in other histological subtypes of epithelial ovarian cancer (90-92).

The effects of SSH on gene expression and phenotypes of OCCC cells have been examined, revealing that multiple genes can be synergistically activated in certain OCCC cells exposed to SSH stress. We first discovered this phenomenon for the *FVII* gene (93) (3 in Fig. 5), which is responsible for initiation of the physiological blood coagulation cascade and a potential contributor to cancer-associated thromboembolism (Fig. 5 and Table III) (94). Unlike typical hypoxia response genes, such as *VEGF*, this transcriptional activation involves an Sp1-HIF2α interaction on the *FVII* gene promoter (Fig. 5) (93). Subsequent studies revealed that multiple genes, including *ICAM1* (95) and *CD69* (96), exhibit the same SSH-driven transcriptional activation (Fig. 5) and have much higher synergism than the *FVII* gene (95,96). We found that unlike hypoxia alone and serum starvation alone, SSH has UPR involvement (Table III) (93). However, the UPR does not contribute to the synergistic expression of *FVII* and *ICAM1* (93,95).

Albumin serves as a major LCFA transporter in the blood and is important for LCFA uptake by cells (97). Addition of albumin-LCFA complex was found to abolish the SSH-driven *ICAM1* and *CD69* expression, suggesting that LCFA starvation is responsible for the synergistic transcriptional activation under hypoxia (95,96) (4 in Fig. 5). Indeed, addition of low-density lipoproteins, including LCFAs and cholesterol as their esterified form, also abolished the SSH-driven *ICAM1* expression (4 in Fig. 5), whereas addition of cholesterol alone did not (98). mTOR is involved in this *ICAM1* expression via NFκB (5 in Fig. 5) (95). Further studies revealed that lipophagy is induced under SSH in OCCC cells and is responsible for the synergistic *ICAM1* and *CD69* expression (6 in Fig. 5) (96,98). Lipophagy enhances binding of pro-inflammatory transcription factor NFκB to the *ICAM1* promoter region via Sam68 and hTERT (7 in Fig. 5) (98). Currently, ICAM-1 is considered to suppress the lipotoxicity-mediated apoptosis induced by lipophagy-driven LD degradation (8 and 9 in Fig. 5 and Table III) (98). Meanwhile, CD69 causes epithelial-mesenchymal transition in a fibronectin-dependent manner (Fig. 5 and Table III), leading to OCCC cell survival *in vitro* and *in vivo* (96).

Adaptive response mechanisms to cholesterol starvation and hypoxia in cancer cells. The effect of SSH on synergistic transcriptional activation in OCCC cells is mediated not only by LCFA starvation but also by cholesterol deficiency. The synergistic *FVII* gene expression under SSH is mediated through activation of the mTOR-SREBP1 axis (10 in Fig. 5) under cholesterol deprivation (11 in Fig. 5) (99). SREBP1 and HIF1α-ARNT complex indirectly promotes *FVII* expression through transcriptional activation of glucocorticoid-induced leucine zipper (GILZ) protein (12 in Fig. 5) to generate procoagulant extracellular vesicles, which are potentially responsible for cancer-associated thromboembolism (Fig. 5 and Table III) (94,99). It is noteworthy that GILZ suppresses SSH-driven *ICAM1* expression because this anti-inflammatory transcriptional regulator binds and inhibits NFkB (13 in Fig. 5) (99).

Glioblastoma cells have been found to exhibit synergistic gene expression mediated by SREBP under both hypoxia and lipoprotein-deficient medium conditions (100). These SSH conditions synergistically enhance transcriptional activation of the lipogenic stearoyl-CoA desaturase, FABP-3, and FABP-4 genes (14 in Fig. 5) to suppress apoptosis and promote spheroid growth (Fig. 5 and Table III). An SREBP-dependent gene signature involving these genes predicts a poor survival rate for patients with glioblastoma (100). Lipogenesis via acetate also supports the survival of cancer cells under SSH, similar to the effect observed with exogenous acetate supply in HeLa cells (82,101). In this process, SREBP2 activates *ACSS2* gene expression to enhance acetyl-CoA production (15 in Fig. 5 and Table III) (101). Additionally, HIFs may contribute to this mechanism because ARNT can upregulate ACSS expression under SSH (Fig. 5 and Table III) (101).

5. Conclusion and perspectives

In recent years, a wealth of knowledge regarding cancer cell metabolism has been accumulated, leading to the proposal of various therapeutic approaches. However, the current understanding of the combined effects of hypoxia and nutrient deprivation on cancer cell phenotypes remains insufficient,

and further research is needed to enhance clinical applications. The conclusion of this review is that cancer cells can adapt to severe oxygenation and nutrient supply conditions through diverse lipid metabolism pathways. Activation of these pathways results in increased malignant phenotypes, including stemness, drug resistance, immune tolerance, and resistance to apoptosis. Thus, in addition to the accumulated information on metabolic reprogramming in cancer, we propose that a detailed understanding of the adaptation mechanisms to both hypoxia and various nutrient starvation conditions provides a platform for exploring promising therapeutic strategies targeting finely reprogrammed metabolisms in cancer. For instance, the suppression of lipid peroxidation correlates with an insufficient supply of multiple AAs, including cysteine, suggesting a potential pro-ferroptosis strategy for treating cancers prone to cysteine starvation. Furthermore, cancer cells rely on multiple lipid metabolism pathways to adapt to GlnD. Thus, combination therapy targeting glutamine supply and lipid metabolism may be promising. Additionally, therapeutic approaches targeting both severe hypoxia and tissue nutrient insufficiency may be beneficial because these harsh tissue conditions are characteristic of tumors. Specific targeting of these tissue conditions is expected to avoid the unwanted adverse effects associated with therapeutic strategies that target hypoxia alone.

Given the contents of the present review, knowledge of the effects of simultaneous deprivation of molecular oxygen and AAs on lipid metabolism in cancer cells has been scarce. Therefore, we propose three new research directions: identification of unaddressed effects caused by depletion of both AAs and lipids, which accelerate malignancy; exploration of cancer types that are highly dependent on lipid metabolism when molecular oxygen and/or nutrients are in poor supply; and identification of biomarkers for such cancer cells and types, which may be vulnerable to lipid metabolism-targeted therapy. Therefore, this preclinical research field currently leaves the door open for greater understanding of tumor biology.

In summary, we have presented a new viewpoint that cancer cells can bypass both hypoxia and nutrient-poor tumor conditions through various types of lipid metabolism. We expect the information in this review to offer insights into how cancer cells adapt to harsh hypoxia and nutrient-deficient conditions, which partially mimic complex tumor microenvironments. Combined with previous studies and future experimental investigations, these efforts are likely to improve the development of new treatment approaches for aggressive cancers, including the identification of novel diagnostic markers and generation of new therapeutic strategies targeting metabolic pathways characteristic to cancer cells exposed to simultaneous insufficiency of molecular oxygen, AAs, and/or lipids.

Acknowledgements

The authors would like to thank Dr Alison Sherwin for editing a draft of this manuscript.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

SK conceived and wrote the manuscript. YM contributed to drafting the manuscript. Data authentication is not applicable. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hanahan D: Hallmarks of cancer: New dimensions. Cancer Discov 12: 31-46, 2022.
2. Pavlova NN, Zhu J and Thompson CB: The hall marks of cancer metabolism: Still emerging. Cell Metab 34: 355-377, 2022.
3. Li F and Simon MC: Cancer Cells don't live alone: Metabolic communication within tumor microenvironments. Dev Cell 54: 183-195, 2020.
4. Koizume S and Miyagi Y: Lipid droplets: A key cellular organelle associated with cancer cell survival under normoxia and hypoxia. Int. J Mol Sci 17: 1430, 2016.
5. Broadfield LA, Pane AA, Talebi A, Swinnen JV and Fendt SM: Lipid metabolism in cancer: New perspectives and emerging mechanisms. Dev Cell 56: 1363-1393, 2021.
6. Riscal R, Skuli N and Simon MC: Even cancer cells watch their cholesterol! Mol Cell 76: 220-231, 2019.
7. Xiang W, Lv H, Xing F, Sun X, Ma Y, Wu L, Lv G, Zong Q, Wang L, Wu Z, *et al*: Inhibition of ACLY overcomes cancer immunotherapy resistance via polyunsaturated fatty acids peroxidation and cGAS-STING activation. Sci Adv 9: eadi2465, 2023.
8. Vanauberg D, Schulz C and Lefebvre T: Involvement of the pro-oncogenic enzyme fatty avid synthase in the hallmarks of cancer: A promising target in anti-cancer therapies. Oncogenesis 12: 16, 2023.
9. Freitas FP, Alborzinia H, dos Santos AF, Nepachalovich P, Pedrera L, Zilka O, Inague A, Klein C, Aroua N, Kaushal K, *et al*: 7-dehydrocholesterol is endogenous suppressor of ferroptosis. Nature 626: 401-410, 2024.
10. Li Y, Ran Q, Duan Q, Jin J, Wang Y, Yu L, Wang C, Zhu Z, Chen X, Weng L, *et al*: 7-Dehydrocholesterol dictates ferroptosis sensitivity. Nature 626: 411-418, 2024.
11. Denko NC: Hypoxia, HIF1 and glucose metabolism in the solid tumor. Nat Rev Cancer 8: 705-713, 2008.
12. Macklin PS, Yamamoto A, Browning L, Hofer M, Adam J and Pugh CW: Recent advances in the biology of tumor hypoxia with relevance to diagnostic practice and tissue-based research. J Pathol 250: 593-611, 2020.
13. Haga N, Saito S, Tsukumo Y, Sakurai J, Furuno A, Tsuruo T and Tomida A: Mitochondria regulate the unfolded protein response leading to cancer cell survival under glucose deprivation conditions. Cancer Sci 101: 1125-1132, 2010.
14. Kwon SJ and Lee YJ: Effect of low glutamine/glucose on hypoxia-induced elevation of hypoxia-inducible factor-1a in human pancreatic cancer MiaPaCa-2 and human prostatic cancer DU-145 cells. Clin. Cancer Res 11: 4694-4700, 2005.
15. Kikuchi D, Tanimoto K and Nakayama K: CREB is activated by ER stress and modulates the unfolded protein response by regulating the expression of IRE1α and PERK. Biochem. Biophys. Res Commun 469: 243-250, 2016.

16. Wang HF, Wang ZQ, Ding Y, Piao MH, Feng CS, Chi GF, Luo YN and Ge PF: Endoplasmic reticulum stress regulates oxygen-glucose deprivation-induced parthanatos in human SH-SY5Y cells via improvement of intracellular ROS. CNS Neurosci Ther 24: 29-38, 2018.
17. Natsuizaka M, Ozasa M, Darmanin S, Miyamoto M, Kondo S, Kamada S, Shindoh M, Higashino F, Suhara W, Koide H, *et al*: Synergistic up-regulation of Hexokinase-2, glucose transporters and angiogenic factors in pancreatic cancer cells by glucose deprivation and hypoxia. Exp Cell Res 313: 3337-3348, 2007.
18. Keith B, Johnson RS and Simon MC: HIF1α and HIF2α: Sibling rivalry in hypoxic tumor growth and progression. Nat Rev Cancer 12: 9-22, 2012.
19. Wouters BG and Koritzinsky M: Hypoxia signalling through mTOR and the unfolded protein response in cancer. Nat Rev Cancer 8: 851-864, 2008.
20. Lee P, Chandel N and Simon MC: Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. Nat Rev Mol Cell Biol 21: 268-283, 2020.
21. Chen J, Kobayashi M, Darmanin S, Qiao Y, Gully C, Zhao R, Kondo S, Wang H, Wang H, Yeung SC, *et al*: Hypoxia-mediated up-regulation of Pim-1 contributes to solid tumor formation. Am J Pathol 175: 400-411, 2009.
22. Liu W, Glunde K, Bhujwalla ZM, Raman V, Sharma A and Phang JM: Proline oxidase promotes tumor cell survival in hypoxic tumor microenvironments. Cancer Res 72: 3677-3686, 2012.
23. Chen X, Ilipoulos D, Zhang Q, Tang Q, Greenblatt MB, Hatziapostolou M, Lim E, Tam WL, Ni M, Chen Y, *et al*: XBP1 promotes triple-negative breast cancer by controlling the HIF1a pathway. Nature 508: 103-107, 2014.
24. Huang C, Li Y, Li Z, Xu Y, Li N, Ge Y, Dong J, Chang A, Zhao T, Wang X, *et al*: LIMS1 promotes pancreatic cancer cell survival under oxygen-glucose deprivation conditions by enhancing HIF1A protein translation. Clin Cancer Res 25: 4091-4103, 2019.
25. Saggese P, Pandey A, Alcaraz M, Fung E, Hall A, Yanagawa J, Rodriguez EF, Grogan TR, Giurato G, Nassa G, *et al*: Glucose deprivation promotes pseudohypoxia and de-differentiation in lung adenocarcinoma. Cancer Res 84: 305-327, 2024.
26. Zhao T, Jiang T, Li X, Chang S, Sun Q, Kong F, Kong X, Wei F, He J, Hao J, *et al*: Nuclear GRP78 promotes metabolic reprogramming and therapeutic resistance in pancreatic ductal adenocarcinoma. Clin Cancer Res 29: 5183-5195, 2023.
27. Nishimoto A, Kugiyama N, Hosoyama T, Enoki T, Li TS and Hamano K: HIF-1α activation under glucose deprivation plays a central role in the acquisition of anti-apoptosis in human colon cancer cells. Int J Oncol 44: 2077-2084, 2014.
28. Takai M, Takauchi M, Kuribayashi M and Tsujiuchi T: LPA receptor-mediated signaling regulates cell motility and survival to anticancer drug of pancreatic cancer cells under glucose-deprived and hypoxic conditions. Biochem Biophys Res Commun 661: 21-27, 2023.
29. Davern M, Fitzgerald MC, Buckley CE, Heeran AB, Donlon NE, McGrath J, O'Connel F, Deshpande MR, Hayes C, MacDonald J, *et al*: PD-1 and TIGIT blockade differentially affect tumour cell survival under hypoxia and glucose deprived conditions in oesophageal adenocarcinoma; implications for overcoming resistance to PD-1 blockade in hypoxic tumors. Transl Oncol 19: 101381, 2022.
30. Buzzai M, Bauer DE, Jones RG, DeBerardinis RJ, Hatzivassiliou G, Elstrom RL and Tompson CB: The glucose dependence of Akt-transformed cells can be reversed by pharmacologic activation of fatty acid β-oxidation. Oncogene 24: 4165-4173, 2005.
31. Leithner K, Triebl A, Trotzmuller M, Hinteregger B, Leko P, Wieser BI, Grasmann G, Bertsch AL, Züllig T, Stacher E, *et al*: The glycerol backbone of phospholipids derives from noncarbohydrate precursors in staved lung cancer cells. Proc Natl Acad Sci USA 115: 6225-6230, 2018.
32. Cai M, He J, Xiong J, Tay LWR, Wang Z, Rog C, Wang J, Xie Y, Wang G, Banno Y, *et al*: Phospholipase D1-regulated autophagy supplies free fatty acids to counter nutrient stress in cancer cells. Cell Death Dis 7: e2448, 2016.
33. Khan AUH, Salehi H, Alexia C, Valdivielso JM, Bozic M, Lopez-Mejia IC, Fajas L, Gerbal-Chaloin S, DaujatChavanieu M, Gitenay D, *et al*: Glucose starvation or pyruvate dehydrogenase activation induce a broad, ERK5-mediated, metabolic remodeling leading to fatty acid oxidation. Cells 11: 1392, 2022.
34. Hoang-Minh LB, Siebzehnrubl FA, Yang C, Suzuki-Hatano S, Dajac K, Loche T, Andrews N, Massari MS, Patel J, Amin K, *et al*: Infiltrative and drug-resistant slow-cycling cells support metabolic heterogeneity in glioblastoma. EMBO J 37: e98772, 2018.
35. Wang C, Haas MA, Yeo SK, Paul R, Yang F, Vallabhapurapu S, Qi X, Plas DR and Guan JL: Autophagy mediated lipid catabolism facilitates glioma progression to overcome bioenergetic crisis. Br J Cancer 124: 1711-1723, 2021.
36. Liu R, Lee JH, Li J, Yu R, Tan L, Xia Y, Zheng Y, Bian XL, Lorenzi PL, Chen Q, *et al*: Choline kinase alpha 2 acts as a protein kinase to promote lipolysis of lipid droplets. Mol Cell 81: 2722-2735, 2021.
37. Chauhan SS, Casillas AL, Vizzerra AD, Liou H, Clements AN, Flores CE, Prevost CT, Kashatus DF, Snider AJ, Snider JM, *et al*: PIM1 drives lipid droplet accumulation to promote proliferation and survival in prostate cancer. Oncogene 43: 406-419, 2024.
38. Cao B, Deng H, Cui H, Zhao R, Li H, Wei B and Chen L: Knockdown of PGM1 enhances anticancer effects of orlistat in gastric cancer under glucose deprivation. Cancer Cell Int 21: 481, 2021.
39. Monteiro-Cardoso VF, Silva AM, Oliveira MM, Peixoto F and Videira RA: Membrane lipid profile alterations are associated with the metabolic adaptation of the Caco-2 cells to a glycemic nutritional condition. J Bioenerg Biomembr 46: 45-57, 2014.
40. Spencer AG, Woods JW, Arakawa T, Singer II and Smith WI: Subcellular localization of prostaglandin endoperoxide H synthase-1 and -2 by immunoelectron microscopy. J Biol Chem 273: 9886-9893, 1998.
41. Roberts HR, Smartt HJM, Greenhough A, Moore AE, Williams AC and Paraskeva C: Colon tumor cells increase PGE2 by regulating COX-2 and 15-PGDH to promote survival during the microenvironmental stress of glucose deprivation. Carcinogenesis 32: 1741-1747, 2011.
42. Hwang SH, Yang Y, Jung JH and Kim Y: Oleic acid from cancer-associated fibroblast promotes cancer cell stemness by stearoyl-CoA desaturase under glucose-deficient condition. Cancer Cell Int 22: 404, 2022.
43. Kamphorst JJ, Nofal M, Commisso C, Hackett SR, Lu W, Grabocka E, Heiden MGV, Miller G, Drebin JA, Bar-Sagi D, *et al*: Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein. Cancer Res 75: 544-553, 2015.
44. Gameiro PA, Yang J, Metelo AM, Perez-Carro R, Baker R, Wang Z, Arreola A, Rathmell WK, Olumi A, López-Larrubia P, *et al*: In vivo HIF-mediated reductive carboxylation is regulated by citrate levels and sensitizes VHL-deficient cells to glutamine deprivation. Cell Metab 17: 372-385, 2013.
45. Kamphorst JJ, Cross JR, Fan J, de Stanchina E, Mathew R, White EP, Thompson CB and Rabinowitz JD: Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. Proc Natl Acad Sci USA 110: 8882-8887, 2013.
46. Miess H, Dankworth B, Gouw AM, Rosenfeldt M, Schmitz W, Jiang M, Saunders B, Howell M, Downward J, Felsher DW, *et al*: The glutathione redox system is essential to prevent ferroptosis caused by impaired lipid metabolism in clear cell renal cell carcinoma. Oncogene 37: 5435-5450, 2018.
47. Byun JK, Choi YK, Kim JH, Jeong JY, Jeon HJ, Kim MK, Hwang I, Lee SY, Lee YM, Lee IK, *et al*: A positive feedback loop between Sestrin 2 and mTORC2 is required for the survival of glutamine-depleted lung cancer cells. Cell Rep 20: 586-599, 2017.
48. Babbar M, Huang Y, An J, Landas SK and Sheikh MS: CHTM1, a novel metabolic marker deregulated in human malignancies. Oncogene 37: 2052-2066, 2018.
49. Juh JW, Yan JB, Lin ZH, Lin SC and Peng IC: SREBP1-induced glutamine synthetase triggers a feedforward loop to upregulate SREBP1 through Sp1 O-GlcNAcylation and augments lipid droplet formation in cancer cells. Int J Mol Sci 22: 9814, 2021.
50. Zhu R, Yang Y, Shao F, Wang J, Gao Y, He J and Lu Z: Choline kinase alpha2 promotes lipid droplet lipolysis in non-small-cell lung carcinoma. Front Oncol 22: 848483, 2022.
51. Guo X, Wang A, Wang W, Wang Y, Chen H, Liu X, Xia T, Zhang A, Chen D, Qi H, *et al*: HRD1 inhibits fatty acid oxidation and tumorigenesis by ubiquitinating CPT2 in triple negative breast cancer. Mol Oncol 15: 642-656, 2021.
52. De Santis MC, Gozzelino L, Margaria JP, Costamagna A, Ratto E, Gulluni F, Gregorio ED, Mina E, Lorito N, Bacci M, *et al*: Lysosomal lipid switch sensitises to nutrient deprivation and mTOR targeting in pancreatic cancer. Gut 72: 360-371, 2023.
53. Kong Y, Wu M, Wan X, Sun M, Zhang Y, Wu Z, Li C, Liang X, Gao L, Ma C, *et al*: Lipophagy-mediated cholesterol synthesis inhibition is required for the survival of hepatocellular carcinoma under glutamine deprivation. Redox Biol 63: 102732, 2023.

54. Nedara K, Reinhardt C, Lebraud E, Arena G, Gracia C, Buard V, Pioche-Durieu C, Castelli F, Colsch B, Bénit P, *et al*: Relevance of the TRIAP1/p53 axis in colon cancer cell proliferation and adaptation to glutamine depletion. Front Oncol 12: 958155, 2022.
55. Lorenz NI, Sittig ACM, Urban H, Luger AL, Engel AL, Munch C, Steinbach JP and Ronellenfitsch MW: Activating transcription factor 4 mediates adaptation of human glioblastoma cells to hypoxia and temozolomide. Sci Rep 11: 14161, 2021.
56. Pan M, Reid MA, Lowman XH, Kulkarni RP, Tran TQ, Liu X, Yang Y, Hernandez-Davies JE, Rosales KK, Li H, *et al*: Regional glutamine deficiency in tumors promotes dedifferentiation through inhibition of histone demethylation. Nat Cell Biol 18: 1090-1101, 2016.
57. Jain M, Nilsson R, Sharma S, Madhusudhan N, Kiytami T, Souza AL, Kafri R, Kirschner MW, Clish CB and Mootha VK: Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. Science 336: 1040-1044, 2012.
58. Gao X, Lee K, Reid MA, Sanderson SM, Qiu C, Li S, Liu J and Locasale JW: Serine availability influences mitochondrial dynamics and function through lipid metabolism. Cell Rep 22: 3507-3520, 2018.
59. Maddocks OD, Berkers CR, Mason SM, Zheng L, Blyth K, Gottlieb E and Vousden KH: Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells. Nature 493: 542-546, 2013.
60. Muthusamy T, Cordes T, Handzlik MK, You L, Lim EW, Gengatharan J, Pinto AFM, Badur MG, Kolar MJ, Wallace M, *et al*: Serine restriction alters sphingolipid diversity to constrain tumour growth. Nature 586: 790-795, 2020.
61. Truman JP, Ruiz CF, Montal E, Garcia-Barros M, Mileva I, Snider AJ, Hannun YA, Obeid LM and Mao C: 1-Deoxysphinganine initiates adaptive responses to serine and glycine starvation in cancer cells via proteolysis of sphingosine kinase. J Lipid Res 63: 100154, 2022.
62. Yun HJ, Li M, Guo D, Jeon SM, Park SH, Lim JS, Lee SB, Liu R, Du L, Kim SH, *et al*: AMPK-HIF-1α signaling enhances glucose-derived de novo serine biosynthesis to promote glioblastoma growth. J Exp Clin Cancer Res 42: 340, 2023.
63. Bonifacio VDB, Pereira SA, Serpa J and Vicente JB: Cysteine metabolic circuitries: Druggable targets in cancer. Br J Cancer 124: 862-879, 2021.
64. Cunningham A, Oudejans LL, Geugien M, Pereira-Martins DA, Wierenga ATJ, Erdem A, Sternadt D, Huls G and Schuringa JJ: The nonessential amino acid cysteine is required to prevent ferroptosis in acute myeloid leukemia. Blood Adv 8: 56-69, 2024.
65. Upadhyayula PS, Higgins DM, Mela A, Banu M, Dovas A, Zandkarimi F, Patel P, Mahajan A, Humala N, Nguyen TTT, *et al*: Dietary restriction of cysteine and methionine sensitizes gliomas to ferroptosis and induces alterations in energetic metabolism. Nature Commun 14: 1187, 2023.
66. Kerimoglu B, Lamb C, McPherson RD, Ergen E, Stone EM and Ooi A: Cysteinase-rapamycin combination induces ferroptosis in both in vitro and in vivo models of hereditary leiomyomatosis and renal cell carcinoma. Mol Caner Ther 21: 419-426, 2022.
67. Liu N, Lin X and Huang C: Activation of the reverse transsulfuration pathway through NRF2/CBS confers erastin-induced ferroptosis resistance. Br J Cancer 122: 279-92, 2020.
68. Armenta DA, Laqtom NN, Alchemy G, Dong W, Morrow D, Poltorack CD, Nathanson DA, Abu-Remaileh M and Dixon S: Ferroptosis inhibition by lysosome-dependent catabolism of extracellular protein. Cell Chem Biol 29: 1588-1600, 2022.
69. Chen PH, Wu J, Ding CKC, Lin CC, Pan S, Bossa N, Xu Y, Yang WH, Mathey-Prevot B and Chi JT: Kinome screen of ferroptosis reveals a novel role of ATM in regulating iron metabolism. Cell Death Differ 27: 1008-1022, 2020.
70. Li Y, Wang X, Huang Z, Zhou Y, Xia J, Hu W, Wang X, Du J, Tong X and Wang Y: CISD3 inhibition drives cysteine-deprivation induced ferroptosis. Cell Death Dis 12: 839, 2021.
71. Liu D, Liang C, Huang B, Zhuang X, Cui W, Yang L, Yang Y, Zhang Y, Fu X, Zhang X, *et al*: Tryptophan metabolism acts as a new anti-ferroptotic pathway to mediate tumor growth. Adv Sci 10: 2204006, 2023.
72. Hong SE, Kim MR, Jang SK, Seong MK, Kim HA, Noh WC, Jin HO and Park IC: Hypoxia suppresses cysteine deprivation-induced cell death via ATF4 regulation in MDA-MB-231 breast cancer cells. Anticancer Res 40: 1387-1394, 2020.
73. Qiu F, Chen YR, Liu X, Chu CY, Shen LJ, Xu J, Gaur S, Forman HJ, Zhang H, Zheng S, *et al*: Arginine starvation impairs mitochondrial respiratory function in ASS1-deficient breast cancer cells. Sci Signal 7: ra31, 2014.
74. Hu Q, Dai J, Zhang Z, Yu H, Zhang J, Zhu X, Qin Y, Zhang L and Zhang P: ASS1-mediated reductive carboxylation of cytosolic glutamine confers ferroptosis resistance in cancer cells. Cancer Res 83: 1646-1665, 2023.
75. Brashears CB, Barlin M, Ehrhardt WR, Rathore R, Schultze M, Tzeng SC, Tine BAV and Held JM: Systems level profiling of arginine starvation reveals MYC and ERK adaptive metabolic reprogramming. Cell Death Dis 11: 662, 2020.
76. Long Y, Tsai WB, Wangpaichitr M, Tsukamoto T, Savaraj N, Feun LG and Kuo MT: Arginine deiminase resistance in melanoma cells is associated with metabolic reprogramming, glucose dependence, and glutamine addiction. Mol Cancer Ther 12: 2581-2590, 2013.
77. Burrows N, Cane G, Robson M, Gaude E, Howat WJ, Szlosarek PW, Pedley RB, Frezza C, Ashcroft M and Maxwell PH: Hypoxia-induced nitric oxide production and tumour perfusion is inhibited by pegylated arginine deiminase (ADI-PEG20). Sci Rep 6: 22950, 2016.
78. Guenin S, Morvan D, Thivat E, Stepien G and Demidem A: Combined methionine deprivation and chloroethylnitrosourea have time-dependent therapeutic synergy on melanoma tumors that NMR spectroscopy-based metabolomics explains by methionine and phospholipid metabolism reprogramming. Nutr Cancer 61: 518-529, 2009.
79. Harada S, Taketomi Y, Aiba T, Kawaguchi M, Hirabayashi T, Uranbileg B, Kurano M, Yatomi Y and Murakami M: The lysophospholipase PNPLA7 controls hepatic choline and methionine metabolism. Biomolecules 13: 417, 2023.
80. Yokogami K, Kikuchi T, Watanabe T, Nakatake Y, Yamashita S, Mizuguchi A and Takeshima H: Methionine regulates self-renewal pluripotency, and cell death of GIC through cholesterol-rRNA axis. BMC Cancer 22: 1351, 2022.
81. Young RM, Ackerman D, Quinn ZL, Mancuso A, Gruber M, Liu L, Giannoukos DN, Bobrovnikova-Marjon E, Diehl JA, Keith B, *et al*: Dysregulated mTORC1 renders cells critically dependent on desaturated lipids for survival under tumor-like stress. Genes Dev 27: 1115-1131, 2013.
82. Li Z, Ji BW, Dixit PD, Tchourine K, Lien EC, Hosios AM, Abbott KL, Rutter JC, Westermark AM, Gorodetsky EF, *et al*: Cancer cells depend on environmental lipids for proliferation when electron acceptors are limited. Nat Metab 4: 711-723, 2022.
83. Qiu B, Ackermann D, Sanchez DJ, Li B, Ochocki JD, Grazioli A, Bobrovnikova-Marjon E, Diehl A, Keith B and Simon C: HIF2α-dependent lipid storage promotes endoplasmic reticulum homeostasis in clear-cell renal cell carcinoma. Cancer Discov 5: 652-667, 2015.
84. Du W, Zhang L, Brett-Morris A, Aguila B, Kerner J, Hoppel CL, Puchowicz M, Serra D, Herrero L, Rini BI, *et al*: HIF drives lipid deposition and cancer in ccRCC via repression of fatty acid metabolism. Nat Commun 8: 1769, 2017.
85. Chen C, Zhao W, Lu X, Ma Y, Zhang P, Wang Z, Cui Z and Xia Q: AUP1 regulates lipid metabolism and induces lipid accumulation to accelerate the progression of renal clear cell carcinoma. Cancer Sci 113: 2600-2615, 2022.
86. Brezis M and Rosen S: Hypoxia of the renal medulla-Its implications for disease. N Eng J Med 332: 647-655, 1995.
87. Little RA, Jamin Y, Boult JKR, Naish JH, Watson Y, Cheung S, Holliday KF, Lu H, McHugh DJ, Irlam J, *et al*: Mapping hypoxia in renal carcinoma with oxygen-enhanced MRI. Radiology 288: 739-747, 2018.
88. Ackerman D, Tumanov S, Qiu B, Michalopoulou E, Spata M, Azzam A, Xie H, Simon MC and Kamphorst JJ: Triglycerides promote lipid homeostasis during hypoxic stress by balancing fatty acid saturation. Cell Rep 24: 2596-2605, 2018.
89. Ji JX, Wang YK, Cochrane DR and Huntsman DG: Clear cell carcinomas of the ovary and kidney: Clarity through genomics. J Pathol 244: 550-564, 2018.
90. Lee S, Garner EIO, Welch WR, Berkowitz RS and Mok SC: Over-expression of hypoxia-inducible factor 1 alpha in ovarian clear cell carcinoma. Gynecol Oncol 106: 311-317, 2007.
91. Anglesio MS, George J, Kulbe H, Friedlander M, Rischin D, Lemech C, Power J, Coward J, Cowin PA, House CM, *et al*: IL6-STAT3-HIF signaling and therapeutic response to the angiogenesis inhibitor sunitinib in ovarian clear cell carcinoma. Clin Cancer Res 17: 2538-2548, 2011.
92. Spowart JE, Townsend KN, Huwait H, Eshragh S, West NR, Ries JN, Kalloger S, Anglesio M, Gorski SM, Watson PH, *et al*: The autophagy protein LC3A correlates with hypoxia and is a prognostic marker of patient survival in clear cell ovarian cancer. J Pathol 228: 437-447, 2012.

93. Koizume S, Ito S, Miyagi E, Hirahara F, Nakamura Y, Sakuma Y, Osaka H, Takano Y, Ruf W and Miyagi Y: HIF2α-Sp1 interaction mediates a deacetylation-dependent FVII-gene activation under hypoxic condition in ovarian cancer cells. Nucleic Acid Res 40: 5389-5401, 2012.
94. Koizume S and Miyagi Y: Tissue factor in cancer-associated thromboembolism: Possible mechanisms and clinical applications. Br J Cancer 127: 2099-2107, 2022.
95. Koizume S, Ito S, Nakamura Y, Yoshihara M, Furuya M, Yamada R, Miyagi E, Hirahara F, Takano Y and Miyagi Y: Lipid starvation and hypoxia synergistically activate ICAM1 and multiple genes in an Sp1-dependent manner to promote the growth of ovarian cancer. Mol Cancer 14: 77, 2015.
96. Koizume S, Kanayama T, Kimura Y, Hirano H, Takahashi T, Ota Y, Miyazaki K, Yoshihara M, Nakamura Y, Yokose T, *et al*: Cancer cell-derived CD69 induced under lipid and oxygen starvation promotes ovarian cancer progression through fibronectin. Cancer Sci 114: 2485-2498, 2023.
97. Trigatti BL and Gerber GE: A direct role for serum albumin in the cellular uptake of long-chain fatty acids. Biochem. J 308: 155-159, 1995.
98. Koizume S, Takahashi T, Nakamura Y, Yoshihara M, Ota Y, Sato S, Tadokoro H, Yokose T, Kato H, Miyagi E, *et al*: Lipophagy-ICAM-1 pathway associated with fatty acid and oxygen deficiencies is involved in poor prognoses of ovarian clear cell carcinoma. Br J Cancer 127: 462-473, 2022.
99. Koizume S, Takahashi T, Yoshihara M, Nakamura Y, Ruf W, Takenaka K, Miyagi E and Miyagi Y: Cholesterol starvation and hypoxia activate the FVII gene via the SREBP1-GILZ pathway in ovarian cancer cells to produce procoagulant microvesicles. Thromb Haemost 119: 1058-1071, 2019.
100. Lewis CA, Peck B, Bensaad K, Griffiths B, Mitter R, Chakravarty P, East P, Dankworth B, Alibhai D, Harris AL and Schulze A: SREBP maintains lipid biosynthesis and viability of cancer cells under lipid- and oxygen-deprived conditions and defines a gene signature associated with poor survival in glioblastoma multiforme. Oncogene 34: 5128-5140, 2015.
101. Schug ZT, Peck B, Jones DT, Zhang Q, Grosskurth S, Alam IS, Goodwin LM, Smethurst E, Mason S, Blyth K, *et al*: Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress. Cancer Cell 27: 57-71, 2015.