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Crosstalk between metabolism and cell death in tumorigenesis

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Abstract

It is generally recognized that tumor cells proliferate more rapidly than normal cells. Due to such an abnormally rapid proliferation rate, cancer cells constantly encounter the limits of insufficient oxygen and nutrient supplies. To satisfy their growth needs and resist adverse environmental events, tumor cells modify the metabolic pathways to produce both extra energies and substances required for rapid growth. Realizing the metabolic characters special for tumor cells will be helpful for eliminating them during therapy. Cell death is a hot topic of long-term study and targeting cell death is one of the most effective ways to repress tumor growth. Many studies have successfully demonstrated that metabolism is inextricably linked to cell death of cancer cells. Here we summarize the recently identified metabolic characters that specifically impact on different types of cell deaths and discuss their roles in tumorigenesis.

Keywords Tumor metabolism, Cell death, Apoptosis, Pyroptosis, Ferroptosis, Cuproptosis, Autophage, Tumor microenvironment

Introduction

Metabolism usually refers to a series of biochemical reactions, which is divided into two categories: catabolism and anabolism [1]. Different metabolic reactions coordinate with each other in vivo to jointly maintain the vital functions of the normal organism. Various substances produced can play a role in signal transductions and participate into various biological processes of the organism. For example, cAMP acts as an important second messenger [2, 3]. According to the differences in types of substrates generated or consumed, metabolism can be divided into carbohydrate metabolism, lipid metabolism,

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amino acid metabolism, nucleotide metabolism, etc. These different metabolic processes are not only involved in the maintenance of body homeostasis, but also associated with the development of diseases. For example, disorders of purine metabolism increase uric acid levels, and the resulted excess uric acidcauses inflammation and further leads to joint swelling [4, 5]. Overall, metabolicdisorders can induce many diseases such as diabetes, hyperlipoproteinemia, hypercalcemia, etc. The metabolism of cancer cells is different from that of normal cells [6]. For example, the Warburg effect is a metabolic process that exists in tumors. It is recognized as a way to gain energy through glycolysis even in the presence of abundant oxygen [7]. Metabolism dysregulation is one of the main hallmarks for the proliferation and invasion of tumors. In the absence of energy, cells may experience a series of function disordersthat even lead to cell death [8].

Cells have a life span and are subject to aging and death, and cell death is inevitable. Based on the different trigger mechanisms and processes, cell death can be divided into apoptosis, necrosis, necroptosis, ferroptosis, pyroptosis, cuproptosis, autophagy, etc. These forms of cell deaths affect the specifically relative cells on their physiological activities and survivals under many different mechanisms. For example, autophagy removes the damaged or senescent organelles by forming autophagosomes [9], while apoptosis is dependent on apoptosomes formation [10]. Cell death can also occur under some stress conditions that are not conducive to cell growth, such as hypoxia, lack of nutrients, or external stimuli. The survival of tumor cells can be affected by targeting cell death-related genes and can further be developed into a strategy for tumor therapy. For example, autophagy can be promoted by suppressing the autophagy-related mTOR pathway [11], thus supporting cancer cells growth. Autophagy not only supports tumor growth, but also can play the role as a tumor suppressor [12]. Under the suppression of MCOLN1/TRPML1, autophagy inhibits tumor metastasis through the TP53/p53 pathway [13]. Targeted cell death is currently used alone or in combination with other types of tumor therapies for cancer treatments [14, 15]. In recent years, as part of the cell death derives from metabolic stress and another part can be involved in metabolic regulation, the relationship between cell death and metabolism has received increasing attention in tumor development and treatment.

The tumor microenvironment is also essential for the development of tumors. The tumor microenvironment is crucial for tumor growth, so changes occurring in this microenvironment largely affects tumor cell survival and growth [16]. The microenvironment is rich and diverse and contains various tumor growth factors, extracellular matrices, and many other types of cells such as immune cells and fibroblasts [17]. These substances participate in tumor growth, development and immune processes [18]. Because of this, the tumor microenvironment has become one of the important targets for tumor therapy. Tumor immunotherapy is a very effective method that includes immune checkpoint therapy and CAR-T therapy, etc. Tumor cells can evade immunological cytotoxicity and immunological surveillance through immune checkpoints such as PD-1/PD-L1 or CTLA-4 [19–21]. For example, PD-1/PD-L1 receptor-ligand interactions are activated to suppress the immune function of T cells in tumors [22–24]. This process is called tumor immune escape [25, 26]. The tumor microenvironment, as the location where tumor cells exist, is involved in various tumor regulatory processes [27]. Immune checkpoint molecules and multiple immune cells, as well as other types of immune molecules present in the tumor microenvironment, make the tumor microenvironment important for immune checkpoint therapy or other immunotherapies [28, 29].

In this review, we will discuss how various metabolic pathways affect different cell death models, mainly focus on the impacts on tumor growths through some crosstalk, which will shed light on the possible connections between metabolic pathways and cell death models within tumor microenvironment. We also hope it will further provide some insights that may help readers investigate the relationships between metabolism and cell death in tumors.

Cell apoptosis affacted by metabolic activities and substrates during tumorigenesis

Apoptosis is one type of programmed cell death that is morphologically characterized by cell shrinkage, compact intracellular arrangement of organelles, nuclear division, and the appearance of apoptotic body in the cytoplasm [30]. Apoptosis is usually classified into two types: the intrinsic pathway and the extrinsic pathway. The intrinsic pathway of apoptosis, also known as the mitochondrial apoptotic pathway, is caused by endogenous apoptotic signals such as endoplasmic reticulum stress, DNA damage, etc. In this pathway, modification of mitochondria structure and function causes apoptosis [30]. The extrinsic pathway of apoptosis is mediated by cell membrane death receptors and exogenous ligands [31]. Apoptosis requires the mediation of a series of key molecules, among which Bcl-2 family proteins and caspase family proteins, etc. play crucial roles. The Bcl-2 family members have different roles in apoptosis. Protein members such as BAX, and BAK have a pro-apoptotic effect, while BCL-2 and BCL-X_L have an inhibitory effect [32]. Caspase proteins such as caspase-9 gain their activity through the cleavage of apoptosome, then involve into the hydrolysis of various intracellular proteins.

One of the most significant changes for tumor metabolism is aerobic glycolysis. Therefore, regulating the enzymes and proteins in glucose metabolism to change energy production rate can effectively modulate tumor growth. Regulation of the activity and function of glucose transporter (GLUT) proteins indeed influences apoptosis and further affects tumor growth [33]. GLUT1 regulates the PI3K/AKT signaling pathways to adjust tumor proliferation and apoptosis [34, 35]. AKT and p53 mutations exist in many different tumor types. Interactions between AKT and p53 in tumor cells affects apoptosis [36]. The p53-inducible gene TIGAR regulates the intracellular fructose diphosphate level. It also reduces the contents of reactive oxygen species to protect cells from ROS-related apoptosis [37]. In similar with the effects of deprivation and glucose metabolism blockage to cause insufficient energy production, abnormal activities of glucose metabolism-related enzymes can also cause this problem to reach to the same levels. For instance, pyruvate kinase, a key enzyme in glycolysis, inhibits apoptosis by supporting glycolysis. Besides repressing key enzymes during glycolysis, key enzymes in the citrate pyruvate cycle such as ATP citrate lyase (ACLY) also regulate apoptosis [38, 39]. In addition, ACLY can be deubiquitinated in the presence of USP30, which regulates the IKKβ-USP30-ACLY signaling axis and further effectively modulates lipid synthesis [40]. These studies show that correlations exist between multiple different metabolic processes and apoptosis. During the same time, many types of carbohydrate metabolism processes may get interactions through certain common enzymes or metabolites (Fig. 1) [41, 42]. Although it has not been fully proved that apoptosis can happen in all types of known carbohydrate metabolisms, it is still expected that the additional metabolic entry points for both regulating apoptosis in tumor cells and further influencing the ongoing tumorigenesis will be finally identified-after the specificities of interactions for different carbohydrate metabolism processes will be clarified.

In addition to carbohydrates, amino acids are also important nutrients as well as important regulatory factors in the organism and tumor development. Similar to glucose, amino acid intakes can also influence apoptosis [43, 44]. Glutamine helps tumors to resist apoptosis, while its deficiency can induce apoptosis [45–47]. Glutamine deficiency and GLS filamentous polymers in cells together lead to asparagine deficiency and ROS-related apoptosis [47]. Other types of amino acids such as proline are also involved in the regulation of tumor cell apoptosis [48, 49]. Similar to glucose metabolism,

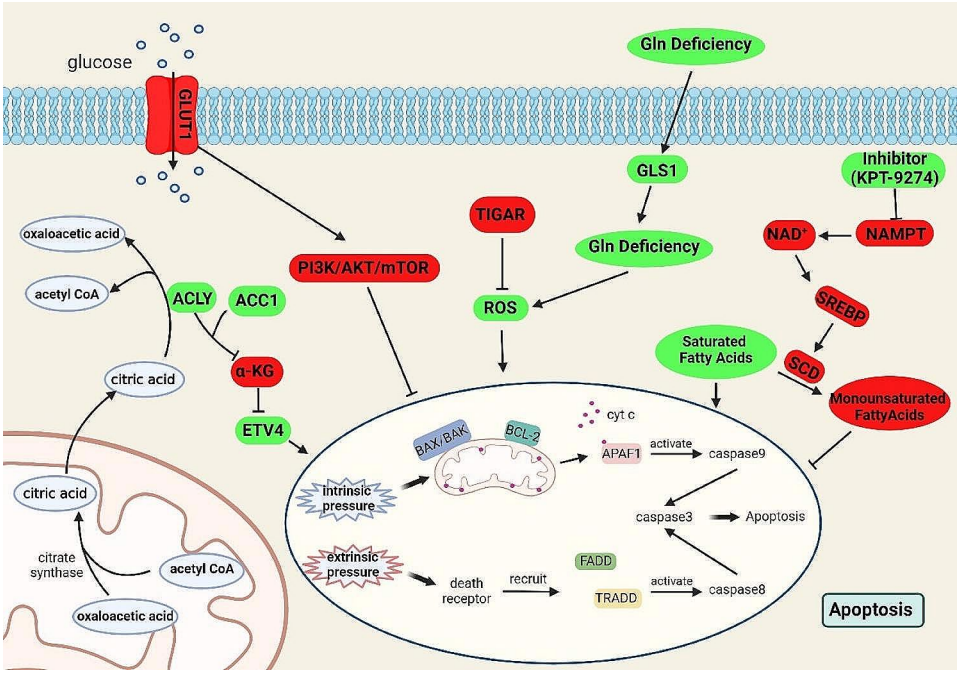

Fig. 1 Metabolites, metabolic pathways and related metabolic genes that play the roles in apoptosis. Deficiencies of various substances involved in metabolism affect the relevant metabolic pathways and apoptosis. Glycolysis can be inhibited in the presence of Glut1 deficiency, which promotes the development of apoptosis. ACLY, a key enzyme involved in the conversion of citric acid to oxaloacetate and acetyl CoA, works with ACC1, an important enzyme in the process of acetyl-CoA production, to regulate the content of α-KG and promote ETV4, which in turn promotes apoptosis. ROS usually promotes apoptosis. When TIGAR inhibits the important oxidative ROS, apoptosis can be suppressed. Gln deletion synergizes with GLS1 to promote ROS-related apoptosis. Inhibition of NAMPT prevents the conversion of saturated fatty acids to monounsaturated fatty acids and promotes apoptosis. The red boxes represent negative regulators and the green boxes represent positive regulators

amino acid transporters also adjust apoptosis in tumors, suggesting that uptake of energy or substances can effectively affect apoptosis. L-type amino acid transporter 1 (LAT1, SLC7A5) is upregulated in many tumors and inhibition of LAT1 function makes cancer cells more sensitive to apoptosis [50, 51]. Besides, some essential amino acids such as phenylalanine and methionine are involved in the regulation of apoptosis (Fig. 1) [52].

Palmitic acid is a highly abundant free fatty acid in the human body and is involved in the regulation of apoptosis [53, 54]. Lipids other than palmitic acid are also involved in the regulation of apoptosis. The oxidized low-density lipoprotein (OX-LDL) is closely related to endothelial cell damage and apoptosis [55, 56]. Besides apoptosis, lipids are also associated with tumorigenesis. ACAT1 acetylates GNAPT to regulate lipid metabolism and promotes hepatocarcinogenesis [57]. SREBP, a key factor in lipid synthesis, has been shown to be involved in apoptosis. SREBP and FASN targeting drugs can inhibit lipid synthesis to induce apoptosis in cancer cells [58]. The SREBP-regulated gene SCD is known to involve into apoptosis. Nicotinamide phosphoribosyltransferase (NAMPT) inhibition can influence on the conversion from the saturated fatty acids to the monounsaturated fatty acids as well as on the expression of SCD, which further have an effect on apoptosis [59]. Other members of the lipid family and lipid metabolic processes have also been shown to be involved in the regulation of apoptosis in various contexts [60–62], demonstrating their indispensable role in regulating tumorigenesis.

Usually, apoptosis can be induced based on the relative mechanisms of either promoting or inhibiting the acquisition of energy. Mitochondria is a vital place for oxidative phosphorylation, which is required by both the aerobic oxidation of glucose and the β-oxidation of triglycerides [63]. Besides, mitochondria is also an important site for regulation of endogenous apoptotic pathway. Thus, modulation of structure and function of mitochondria of tumor cells can induce their apoptosis [64, 65]. Taken together, these studies suggest that it is feasible to influence tumor cell apoptosis through metabolism, either by directly reducing nutrient intake or affecting cellular nutrient utilization (Fig. 1). Tumor cell apoptosis regulated by metabolism does not just inhibit tumorigenesis, sometimes it appears to promote tumor growth. We may use this as a starting point to find more methods that can effectively inhibit tumorigenesis.

The crosstalk between metabolism and necrosis during tumorigenesis

Cell necrosis is defined as a pathological injury that is caused by factors such as physical damage, chemical stimulation or hypoxia. One of the most significant morphological features of necrosis is the rupture of cell membrane [66]. Due to the broken membrane, intracellular inflammatory substances are released into the surrounding environment and further induce an inflammatory response. Necrosis is a very common phenomenon in tumors [67]. Since the formation of blood vessels cannot keep up with a rapid expansion of the tumor tissue volume, a remarkable feature of solid tumors is that the internal tumor tissue is often devoid of oxygen and nutrients, thus making it more prone to necrosis.

Glucose metabolism is an important regulatory activity for tumors. It affects tumor growth by regulating apoptosis, autophagy, and other different kinds of cell deaths. Inhibition of glucose uptake is an important trigger for tumor necrosis, as cancer cells are more inclined to use glucose for glycolysis to gain energy [68]. During the process, the genes relative to energy metabolism is used as the inducing targets to regulate cell death. The transcription factor ATF4 also plays a role in necrosis that is regulated by glucose deprivation [69]. ATF4 is associated with p53 in different signaling pathways and influences the onset of other types of cell death in tumors [70, 71]. P53 also upregulates the expression of the lncRNA TRINGS in the context of glucose deficiency, allowing the increased TRINGS to bind STRAP for inhibiting STRAP mediated necrotic signaling [72]. Besides low glucose, high glucose levels can also regulate necrosis in many situations (Fig. 2) [73–77], demonstrating the broad role of glucose in regulating necrosis.

Specific types of amino acids can promote tumor necrosis and achieve anti-tumor effects. Such amino acid induced necrosis occurs in prostate tumors [78]. Besides nutrients, other factors also regulate necrosis, such as hypoxia and reactive oxygen species [79, 80]. Hypoxia is an important necrosis inducing factor and converts the glucose deprivation-induced necrosis into AKT-dependent apoptosis [81]. As energy deficiency itself is one critical reason for tumor necrosis, we can curb the uptake and utilize of energy substances to induce necrosis [82, 83]. As a form of cell death that can be modulated by energy stress, it is feasible to influence necrosis in tumor cells through modulating energy-generating or depleting pathways.

The function of metabolism and necroptosis during tumorigenesis

Necrosis was once not considered to be regulated by genetics, but in subsequent studies, necrosis has been discovered as a gene-regulated cell death and designated necroptosis. Necroptosis is triggered by many protein kinases, including RIPK3, MLKL as well as other critical kinases [84]. Apoptosis-inducing receptors such as FAS, TNF receptor 1 (TNFR1), TNFR2, etc. also play a role in necroptosis. In addition, immune molecules associated with damage-associated molecular patterns (DAMP)

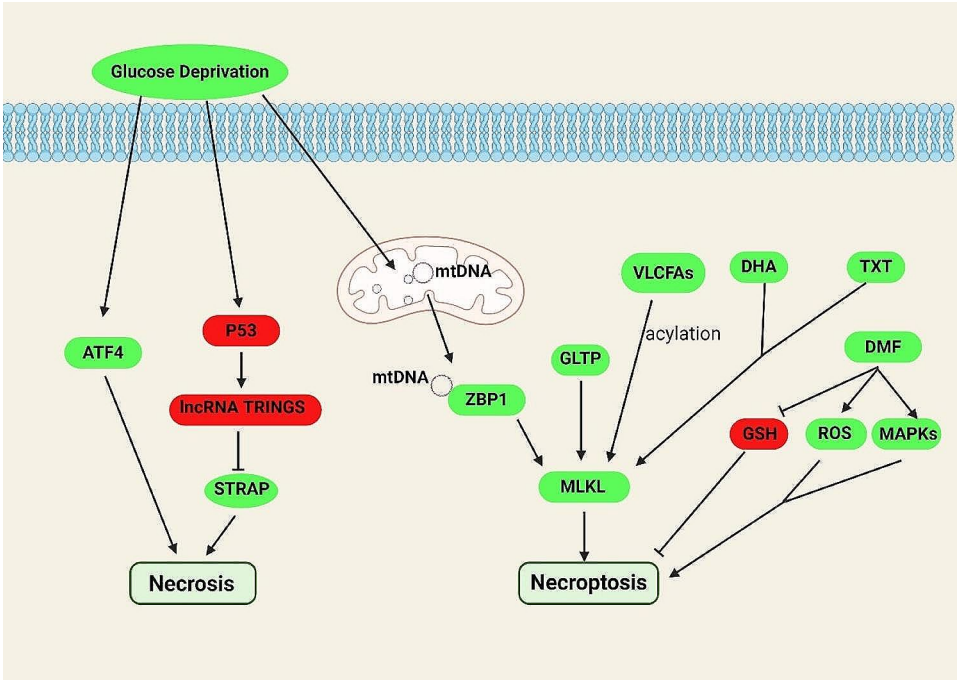

Fig. 2 Metabolites, metabolic pathways and related metabolic genes that take part in necrosis and necroptosis. Glucose starvation promotes necrosis through the transcription factor ATF4. In addition, it can act on p53, which regulates necroptosis by affecting the interaction between TRINGS and STRAP. Glucose deprivation also facilitates necroptosis by promoting the binding of mitochondrial DNA and ZBP1 to regulate MLKL, a key substance in the development of necroptosis. DHA supplementation with docetaxel (TXT) promotes necroptosis. As one of the key components of the necrosome that promotes the onset of necroptosis, MLKL function can be facilitated by GLTP. Very long chain saturated fatty acids participate in necroptosis by targeting MLKL. DMF promotes necroptosis by promoting the depletion of GSH, ROS generation and MAPK activation. The red boxes represent negative regulators and the green boxes represent positive regulators

stimulates the recognition receptors (PRRs) and leads to necroptosis [85]. Necroptosis as the regulated cell death mode is studied for its application in tumor therapy [15]. Necroptosis associated ZBP1 is regulated by the RNA editing enzyme ADAR1, thus affecting the actual efficacy of immune checkpoint blockade therapy [86]. During tumor prognosis, it has been shown that necroptosis promotes tumor repopulation after the treatment through RIP1/RIP3/MLKL/JNK/IL8 signaling pathway (Fig. 2) [87].

MLKL is one of the key regulators of necroptosis. Several studies have already uncovered the link between MLKL and energy stress, which provides good concept for the metabolic regulation of necroptosis. For example, overexpression of GLTP, a protein involved in the transport of sphingomyelin, induces phosphorylation of MLKL and leads to necroptosis [88]. Meanwhile, after glucose deprivation, ZBP1 is found to activate MLKL and promotes necroptosis in breast cancer cells [89]. Some substances, such as the members of the lipid family, can individually affect necroptosis. Docosahexaenoic acid (DHA), a member of the lipid family, is also related to necroptosis. DHA supplementation with docetaxel (TXT) promotes necroptosis in breast cancer cells [90]. Very long chain saturated fatty acids can also participate in the induction of necroptosis by regulating protein acylation [91]. In addition to the lipid, necroptosis with glutathione participation has also been reported. Dimethyl fumarate (DMF) can induce necroptosis by depleting GSH in colon cancer cells [92]. Moreover, AMPK of glucose dependent kinase regulates necroptosis and tumorigenesis through the activations of RIPK3 [93]. In addition, RIPK3 also links energy metabolism to necrosis and apoptosis [94], suggesting that energetic factors play an important role in RIP3-associated necroptosis. RIPK3 has been studied broadly as a crucial regulator of programmed cell death during tumorigenesis [95–97], and considered as an effective target for blocking tumorigenesis.

The metabolism and ferroptosis in cancer

Ferroptosis is an iron-dependent programmed cell death, which is mainly manifested by extensive peroxidation of lipid bilayers. Unlike other cell death processes, ferroptosis is dependent on iron accumulation and lipid peroxidation [98]. Ferrous irons play a critical role in promoting phospholipid peroxidation, which in turn enhances ferroptosis. Phospholipids are also over-oxidized under the actions of reactive oxygen species, which cause irreversible damage to the cell membrane [99].

Both substances and key enzymes of lipid metabolism have been found to participate in the occurrence and development of tumors through affecting ferroptosis [100, 101]. Lipid family members such as polyunsaturated fatty acids are known to induce ferroptosis [102], suggesting that it may be feasible to influence both ferroptosis and ferroptosis-related tumor growth through regulating lipid content. In addition, enzymes of fatty acid metabolism and lipid transport also play a role in the regulation of tumor ferroptosis. It is well demonstrated that ferroptosis and further tumorigenesis can be regulated by lipid metabolism alteration. Stearoyl-CoA desaturase 1 (SCD1), a key enzyme in the conversion of saturated fatty acids to monounsaturated fatty acids, plays an important role in regulating the lipid metabolism related to ferroptosis [103]. Inhibition of stearoyl-CoA desaturase reduces the levels of membrane antioxidant CoQ10 and promotes ferroptosis in ovarian cancer cells [104, 105]. SCD1 and fatty acid binding protein 4 (FABP4) contribute to the resistance to ferroptosis during tumor recurrence [106]. Moreover, it has been shown that SCD1 is also involved in the regulation of ferroptosis in several cancers, including gastric, ovarian, and colon cancers [107–109]. Members of the SREBP family that are involved in cholesterol metabolism also participate in the regulation on ferroptosis [110]. In some cancers, activation of the PI3K/AKT/mTOR signaling pathway resists ferroptosis through controlling the activities of sterol regulatory element-binding proteins 1 (SREBP1) and SCD1. Activation of PI3K/AKT/mTOR signaling pathway affects the binding between SREBP1 and mTOR, further activating downstream SCD1 to promote lipid synthesis to defend against ferroptosis [108]. SREBP2 reduces both intracellular iron content and lipid peroxidation through transcriptionally regulating transferrin (TF), thereby resisting ferroptosis [111]. Ferroptosis can be promoted when the peroxisome proliferators-activated receptors (PPARs) activity is affected by the p53 regulator MDM2 and MDMX [112–115]. PPARα also regulates ferroptosis by affecting FABP1 [116]. Besides, lipid molecules impacts ferroptosis [117, 118]. Energy metabolism genes such as AMPK play a vital role in the regulation of tumor ferroptosis [119, 120]. Therefore, tumor ferroptosis can be effectively controlled through metabolism regulation (Fig. 3).

Ferroptosis is inseparable from lipid peroxidation. Glutathione as an important reductant in organisms plays a critical role in the process of anti-oxidation. Several substances that are either related to glutathione are known to be involved in ferroptosis [121, 122]. Consumption of glutathione is one of the necessary conditions for ferroptosis [123, 124]. Glutamine is one of the raw materials for the synthesis of glutathione. Attenuated glutamine

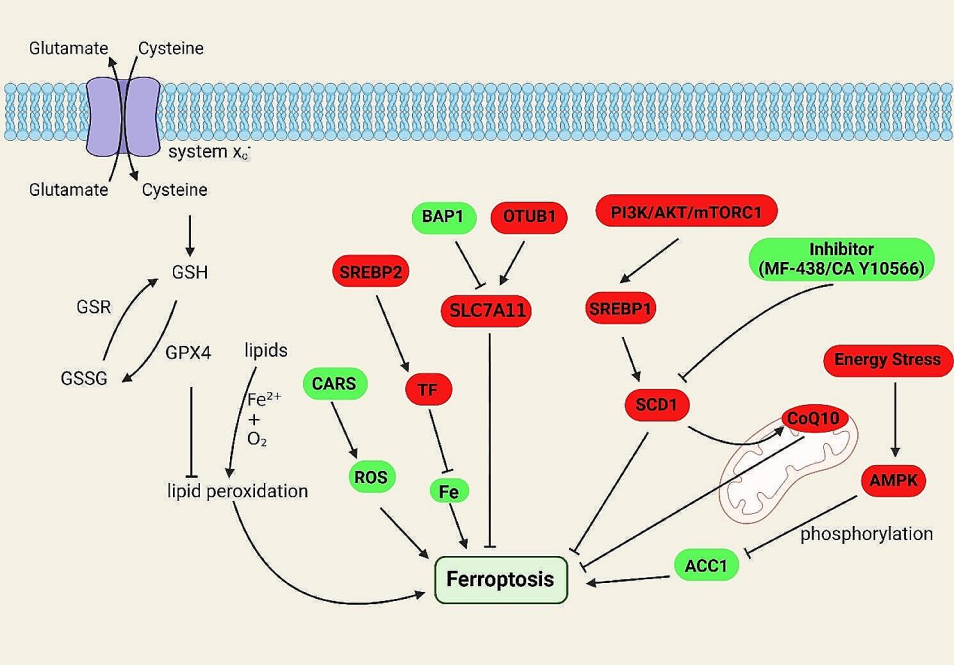

Fig. 3 Metabolites, metabolic pathways and related metabolic genes that play the roles in ferroptosis. Lipid oxidation is an important process in ferroptosis and requires the participation of iron. Upregulation of ROS levels by CARS promote ferroptosis, while downregulation of iron ion levels by SREBP2 and TF inhibit ferroptosis. Besides, PI3K/AKT/mTORC signaling pathway activates lipid synthesis-related SREBP1 and SCD1, then affect lipid synthesis to inhibit ferroptosis. While inhibition of SCD1 can influence CoQ10 which locate on the mitochondrial electron transport chain and promote ferroptosis. BAP1 promotes ferroptosis by inhibiting the cystine transport-related SLC7A11, while OTWB1 exerts the opposite effect. Energy stress regulates ACC1 via AMPK, reducing ACC1 activity and inhibiting ferroptosis. The red boxes represent negative regulators and the green boxes represent positive regulators

catabolism inhibits ferroptosis and reduces its damaging effect on cardiomyocytes [125]. Glutathione is converted intracellularly to GSSG to resist ferroptosis. In addition to regulating glutathione levels, the cellular uptake of cysteine can also be targeted to promote or inhibit ferroptosis. Cysteine deprivation in the mouse pancreatic ductal adenocarcinoma model leads to ferroptosis and inhibits tumor cell growth [121]. The incidence of ferroptosis is increased significantly after the exchanges between cystine and glutamate inhibited by the anticancer drugs [126]. Many cysteine transporters, such as Cysteinyl-tRNA synthetase (CARS) and SLC7A11, involve in tumor ferroptosis [122, 127]. Meanwhile, the stability and expression of SLC7A11 is affected by OUTB1 and BAP1 to promote or inhibit tumor ferroptosis [128, 129]. Therefore, Glutathione is an important target to regulate tumor growth associated with ferroptosis [130–132]. Taken together, we may be able to extend the effects of lipid metabolism and glutamine metabolism on ferroptosis to other metabolic types through these intersections to identify additional ferroptosis regulatory targets.

The function of metabolism and pyroptosis during tumorigenesis

Pyroptosis is defined as inflammatory cell death, which depends on the Gasdermin family of proteins and inflammatory caspase. Many factors can induce pyroptosis, such as bacterial, viral infections, and energy stress et al. [133]. Lipids such as docosahexaenoic acid (DHA) change the GSDMD activity to influence pyroptosis [134]. During pyroptosis, some proteins related to lipid metabolism, such as Fatty acid binding protein 4 (FABP4), play a role [135]. GPX4 is related to lipid peroxidation and also regulates pyroptosis. Loss of GPX4 upregulates the generation of GSDMD N-terminals by activating caspase11, then promotes pyroptosis [136]. The low-density lipoprotein receptor (LDLR) and lipids related to cholesterol transport play a role in the regulation of tumor pyroptosis [137]. LDLR negatively regulates the activity of the inflammasome NLRP3 and inhibit the inflammatory response, while the absence of LDLR is conducive to pyroptosis (Fig. 4) [138].

Energy stress is one of the most significant cellular environment factors that induces the cells to enter into pyroptosis [139, 140]. For example, the protein SGLT2, related to glucose transport, is involved in the regulation of NLRP3 activity [140]. In addition to glucose, fatty acids also take part in the regulation of inflammasome activity [141]. NLRP3 is regulated by metabolism-related substances, but is also involved in obesity-related inflammation [142]. Pyroptosis occurs not only in tumors but also in infectious and metabolic diseases. As a regulated death, current interest in pyroptosis is mainly in inflammatory vesicles and members of the gasdermin family. The role of metabolic regulation in pyroptosis has been gradually uncovered, and many metabolites also

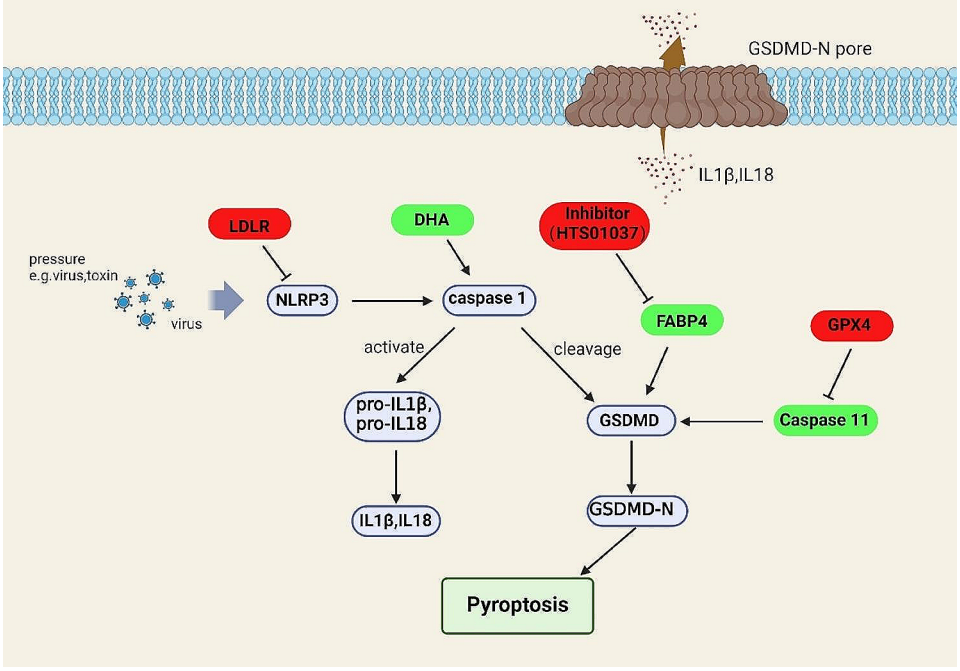

Fig. 4 Metabolites, metabolic pathways and related metabolic genes that play the roles in pyroptosis. NLRP3 plays an important role in the process of pyroptosis, which inhibition of NLRP3 will lead to the downregulation of pyroptosis. LDLR inhibits pyroptosis by mediating NLRP3. DHA promotes pyroptosis through affecting caspase1, and FABP4 exert the same effect through activating GSDMD. GPX4 inhibit pyroptosis by affecting the processing of GSDMD by caspase11, respectively. The red boxes represent negative regulators and the green boxes represent positive regulators

participate in inflammatory response. It is expected more findings will be demonstrated that metabolism influences tumorigenesis by regulating pyroptosis.

The cuproptosis is a new role of metabolism during tumorigenesis

Copper death has been recently defined as a new type of cell death [143]. It is induced under the action of the copper ionophore elesclomol [143, 144]. During the process, excessive accumulation of copper ions promotes the oligomerization of fatty acylated proteins dihydrolipoamide Sacetyltransferase (DLAT) and FDX1-related Fe-S cluster proteins in the tricarboxylic acid cycle [143]. The Fe-S cluster proteins associate with FDX1 to become the important components of the electron transport chain [145]. Cuproptosis is down-regulated after the function of ETC suppressed by respiratory chain complexes I and III inhibitors [146], suggesting that ETC is another copper death-regulating target in addition to TCA [143, 147]. After cuproptosis is formally defined, several types of relationships between cuproptosis and tumorigenesis have been discovered. For example, the lncRNAs analysis that are related to cuproptosis to obtain the relevant expression profiles is an effective way to determine the possibility of prognosis [148, 149]. Recent studies include thatcuproptosis-related genes are also associated with cancer prognosis [150–152]. In particular, we performed the differential expression analysis and survival analysis of cuproptosis-related genes in colorectal cancer and hepatocellular carcinoma, and found that there are different expression and survival outcomes (Figs. 5 and 6). Since cuproptosis is dependent on the accumulation of copper ions and lipid-acylated proteins in the tricarboxylic acid cycle, we might be able to regulate the tricarboxylic acid cycle by modulating intracellular copper ion metabolism [143, 153]. Therefore, controlling the occurrence and development of a particular metabolic process can regulate the production of specific intermediates and result in an effect on the tricarboxylic acid cycle and cuproptosis.

Autophagy derived from metabolic activities during tumorigenesis

Autophagy is defined as a process that is lysosome dependent, which is featured by the generation of autophagosome [9]. Autophagosomes then fuse with lysosomes to form autolysosomes, and lysosome-carried enzymes can finally hydrolyze the material inside the autophagosome [154]. Since autophagy is also a process of energy reuse, it can be upregulated in response to the needs of cellular

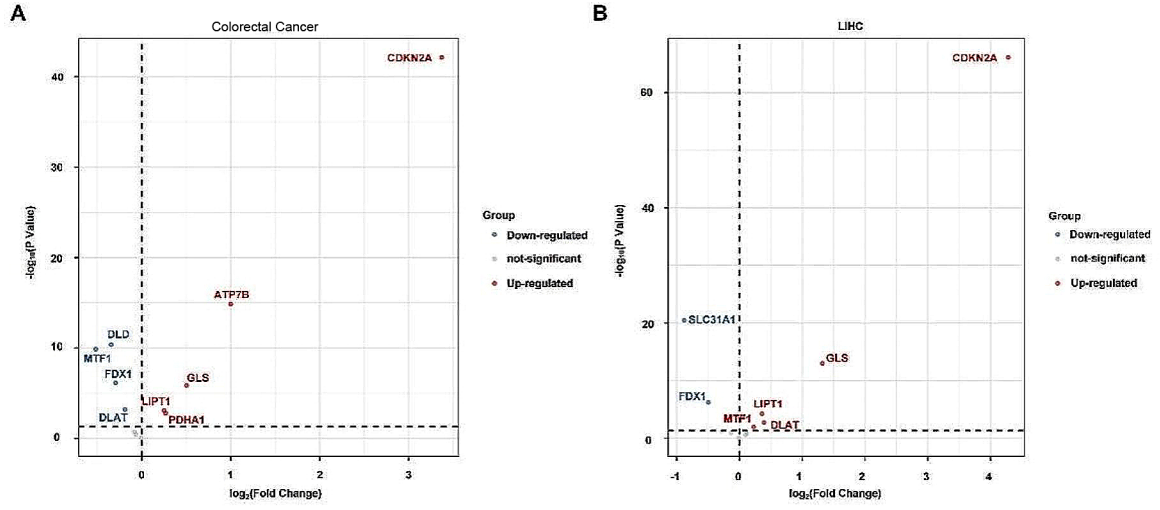

Fig. 5 The expression levels of cuproptosis genes in colorectal cancer and hepatocellular carcinoma. (A and B) The expression levels of cuproptosis genes in colorectal cancer (A) and hepatocellular carcinoma (B). The blue dot represents the genes that are down-regulated in cancer, the red dot means these genes are up-regulated in cancer ($p < 0.05$), and those with no significant difference compared with normal tissues are indicated in gray. Both mRNA Seq data and clinical data collected from TCGA database, including COAD, READ and LIHC reveal that the COAD and READ are merged into colorectal cancer based on gene names. In the mRNA differential expression analysis, the R package Deseq2 was used to differential expression analysis. The genes with a fold change (FC) > 0 and an adjusted P-value (FDR) > 0.05 were retained for further analysis

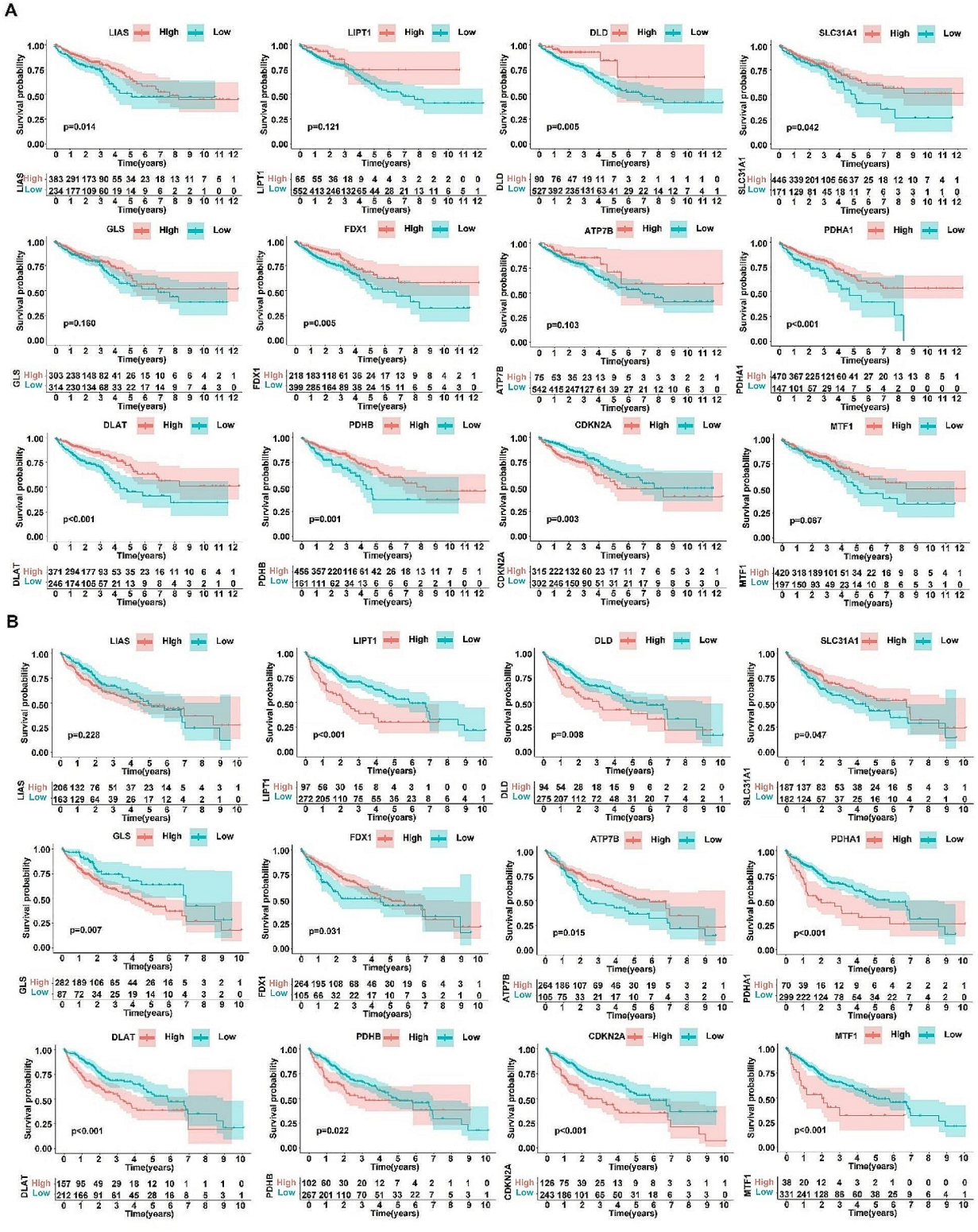

Fig. 6 (See legend on next page.)

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Fig. 6 Survival analyses of cuproptosis-related genes in both colorectal cancer and hepatocellular carcinoma. (A and B) The survival analysis of cuproptosis-related genes in colorectal cancer (A) and hepatocellular carcinoma (B). The top part of the survival analysis for each gene shows the Kaplan-Meier survival curves for the genes obtained by the optimal division method, with the red and blue lines representing the high and low expression groups based on gene expression levels, and the horizontal coordinate (Time(years)) representing the survival time and the vertical coordinate (Survival probability) representing the survival rate. In the bottom part of the graph, the horizontal coordinate Time (years) represents the follow-up time, and the optimal division method divides all patients into high and low expression groups at the beginning of the follow-up period. The mRNA expression data of genes and corresponding clinical survival data across colorectal cancer and LIHC were merged for expression survival analysis. Tumor samples were divided into high and low groups according to median gene expression value. The R package survival was used to fit the survival time and survival status for the two groups. Differences in P value were examined in the survival outcomes of the groups according to Kaplan–Meier survival analysis

life activities under certain conditions, such as starvation and glucose deprivation [155]. During the process related to glucose metabolism, Akt is associated with various enzymes in glycolysis to influence autophagy. Inhibition of PFKFB3 expression in the presence of Akt inhibition attenuates the rasforin-induced autophagy in gastric cancer cells [156]. Besides, Akt also affects autophagy through regulating the activity of hexokinase [157]. Hexokinase-II inhibits mTOR to regulate glucose deprivation induced autophagy [158]. mTOR is an important negative regulator of autophagy, and it is also involved in the regulation of various metabolic activities, especially insulin-mediated glucose metabolism [159]. Promotion or inhibition autophagy of amino acids by regulating mTOR is a proven truth [160, 161]. Amino acids depletion inhibits mTOR through p27, thereby promotes autophagy [162]. AMPK also takes part in tumor autophagy [163]. AMPK phosphorylates mammalian autophagy-related Unc-51-like kinase (ULK1) under low-energy conditions to promote autophagy [164, 165]. In addition, large numbers of non-tumor cells are present in the tumor microenvironment. These cells can secrete various factors such as growth factors and immune factors. One of the adipocyte products, ADIPOQ/adiponectin, activates AMPK via STK11/LKB1. The activated AMPK can further promote autophagy in breast cancer cells by activating ULK1 [166]. In the absence of glucose, AMPK also mediates GAPDH nuclear transfer to activate Sirt1 and promotes autophagy (Fig. 7) [167].

The function of amino acids in autophagy has been thoroughly reported in recent years. Loss of glutamine promotes two important activities to lead to autophagy, including the acetylation of PGK1, and the phosphorylation of Beclin1 [168]. During cancer radiation therapy, cancer cells that are resistant to glutamine depletion can induce autophagy through activating ATG5 to defend against radiation-induced damage [169]. In addition to glutamine, other amino acids can also regulate autophagy [170–175], suggesting that tumor autophagy and tumorigenesis can be effectively regulated by changing amino acid levels or metabolic processes in vivo.

Besides the glucose and amino acids, the lipid affected autophagy regulation also has been found recently [176, 177]. The AMPK/mTORC signaling pathway plays an important role in the lipid-related autophagy, indicating that the lipid-regulated tumor autophagy could also associate with AMPK/mTORC [178–181]. Besides, autophagy can reversely affect lipid metabolism under various situations. For example, autophagy causes degradation, formation, and accumulation of lipid droplets [182]. Deletion of autophagy-related genes induces intracellular lipid accumulation in non-small cell lung cancer models [183]. In addition, autophagy-related genes such as ATG5 and ATG7 are also involved in metabolic regulation and metabolism-related tumor therapy [184–187]. Taken together, autophagy and autophagy-associated proteins are regulated in a variety of metabolic situations and can likewise control metabolism in tumorigenesis.

Metabolism, cell death and tumorigenesis

As one of the most important physiological activities of cells, metabolism not only regulates cellular energy status, structure and function, but also participates in a variety of important intracellular modifications. Generally, metabolic stress and metabolite-related transporters can involve in tumor regulation. Energy supplies the basis power for all life activities, but tumors have higher energy requirements than normal tissues [188]. Glucose transporters effectively alter the processes of tumor cell glucose metabolism and regulate tumorigenesis [33, 189, 190]. The amino acid transporters are also associated with tumorigenesis. Cystine transporter SLC7A11 transports cystine across the cell membrane to participate in glutathione biosynthesis to regulate tumorigenesis [191, 192].

Metabolism is also closely linked to post-translational modifications such as glycosylation, palmitoylation, and lactylation. Different types of glycosylations activate or stabilize the function of biomolecules and regulate tumorigenesis and tumor growth [193–195]. Previous studies have discovered that palmitoylation affects the development of melanoma, lung cancer and other tumors [196–198]. Lactylation can likewise affect tumorigenesis and progression [199–201]. Hypersuccinylation, another product of glucose metabolism, is associated with the TCA cycle to inhibit mitochondrial respiration and induces apoptosis and tumor development [202].

Metabolism and cell death are the two vital life activities in cells. For example, cuproptosis, a newly defined cell death model, contributes to cell death by affecting

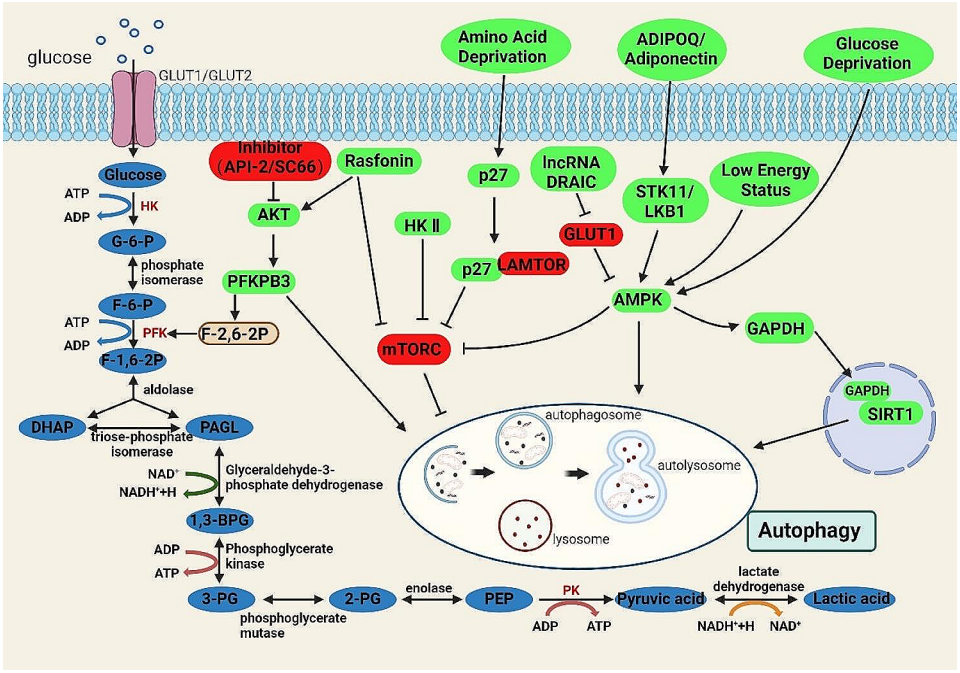

Fig. 7 Metabolites, metabolic pathways and related metabolic genes that work in autophagy. mTORC is an important negative regulator of autophagy, and many factors promote autophagy by inhibiting mTORC. Rasfonin regulates autophagy both through AKT and mTORC. Amino acid deprivation inhibits mTORC through p27, its combination with LAMTOR in turn accelerates autophagy. Hexokinase II can inhibit mTORC, thus promoting autophagy. AMPK can also inhibit mTORC under the regulation of lncRNA DRAIC. Under low energy state stimulation of AMPK can promote autophagy. The STK11/LKB1-AMPK axis also exerts a pro-autophagic effect by affecting AMPK. Glucose deprivation promotes nuclear translocation of GAPDH and binding to SITR1 via AMPK, which in turn promotes autophagy. The red boxes represent negative regulators and the green boxes represent positive regulators

the TCA cycle [203]. Copper ion is an essential trace element, which is not only related to intracellular oxidation-reduction property, but also acts as one of the main triggers of cuproptosis. Copper ions implicates a variety of intracellular activities, such as redox reactions and the mitochondrial respiratory chain. Disturbances in copper ion metabolism leads to the well-known Wilson's disease [204], on the other hand, depletion of copper ions in mitochondria is associated with tumor suppression [205]. Ferroptosis is another trace element-dependent cell death closely related to amino acid metabolism [206]. Ferroptosis also requires phospholipid peroxide that is a product of lipid metabolism and redox reaction [206], and through excessive accumulation of lipid peroxide it causes cell death.

The secondarily considered link between metabolism and cell death is that multiple cell death regulators are also the energy sensors. AMPK is an important intracellular energy receptor. AMPK activates downstream molecules and promotes energy production after it either senses a rise in the ADP/ATP ratio [207], or inhibits energy-consuming processes such as the synthesis of biomolecule glycogen. AMPK implicates in metabolic diseases as an important energy sensor and regulator [208]. Energy stress is a potent inducer of cell death, and RIPK1 induces cell death under energy stress, whereas AMPK inhibits RIPK1 and metabolic stress-induced RIPK1-associated cell death by phosphorylation [209]. mTOR is also a very important autophagy regulatory molecular [210–212]. AMPK/mTOR together regulate tumorigenesis and tumor progression in both lung and colorectal cancers [213, 214], demonstrating their combined contribution to metabolism and cell death for tumorigenesis.

Metabolites are the intersection between metabolism and cell death, which also modulate cell death. For example, α-KG, an intermediate of the TCA cycle, recruits pro-caspase-8 and GSDMC in acidic environments and activates pyroptosis [137]. Certain metabolites released by cell death also perform functions to modulate peripheral immune or inflammatory responses [215, 216]. Metabolites released by apoptosis can alter the gene expression of myeloid cells and attenuate inflammatory responses [217]. Some cell death releases inflammatory substances into the environment and causes severe inflammatory response. NLRP3 inflammasome activation, such as IL-1β and IL-18 production, promotes immune cell infiltration in the tumor microenvironment and enhances chemotherapy-induced anti-tumor immunity [218, 219].

Regulated Cell Death (RCD) used to be considered non-immunogenic. However, an Immunogenic Cell Death (ICD) related to tumor immunity has been

proposed after sufficient investigations with more research on cell death patterns [220]. ICD occurs with Damage-Associated Molecular Patterns (DAMPs) release or exposure of some immunogenic substances during cell death [220, 221]. A series of stresses such as radiation, viruses and ischemia promote DAMPs release into the extracellular environment [221]. As an effective immune activator, DAMPs then combine with its receptor and further promote inflammation [220]. ICD is thought to modulate the tumor immune microenvironment and is one of the targets for tumor immunotherapy [222]. Many cell death models exert immunogenic potential in tumors and influence tumorigenesis and development by activating the tumor immune response.

Immune system can activate ferroptosis. Interferon gamma (IFNγ) released by $CD8^+$T cells in the tumor microenvironment restrains cystine uptake, and tumor cells deficient in cystine have difficulty in resisting lipid peroxidation and thus promote ferroptosis [223]. In turn, ferroptosis that occurs in tumor cells acts inversely on the immune system and promotes the development of immune cells [224]. Cell death models such as ferroptosis, pyroptosis and cuproptosis can influence the immune infiltration of TME [225]. These cell death patterns affect immune cell infiltration [219] and expression levels of immune checkpoint molecules [226], ultimately regulating tumor survival and progression by activating or suppressing the tumor immune response.

TME, metabolism and cell death

One of the most significant effects of TME on tumor metabolism is that it regulates the rate of tumor cell glucose metabolism. In oxygen-deficient TME, the PI3K/Akt/HIF-1α signaling axis is activated and further regulates the process of glycolysis [227], and the alteration of HIF-1α and glycolysis promote the proliferation of tumor cells. The high rate of glycolysis in tumor cells leads to the production of large amounts of lactate, which is transported outside the cell and then accumulates in the environment leading to a decrease in pH and creating an acidic tumor microenvironment [228]. A low pH environments has been demonstrated that can induce necrosis and apoptosis [229]. Since there are many different types of cells present in the TME, the buildup of lactate can regulate the function of these cells. Previous studies demonstrates that lactate promotes M2 macrophage polarization in TME and facilitates pituitary adenoma (PA) invasion [230]. Tumor-associated macrophages are a class of cells with high presence in the tumor microenvironment and are thought to be associated with the regulation of cellular metabolism [231, 232]. It is thought to be associated with the regulation of iron levels [233], while high iron content is considered to be another conducive condition for ferroptosis. Other immune cells enriched in the TME and their immune functions are also regulated by lactate, which leads to tumor immune escape by altering the immune environment. Firstly, high levels of lactate are inherently immunosuppressive [200]. The acidic environment caused by lactate interferes with the lactate metabolism of T cells via monocarboxylate transporter 1 (MCT1) and inhibits the proliferation of T cells [234]. Moreover, the absence of MCT1 in Treg cells not only inhibits tumor growth, but also accompanies the high expression of immune checkpoint molecules [235]. Secondly, lactate represses T cell by modulating the expression of immune checkpoint molecules PD-1 and PD-L1, which causes immune escape. Lactate restrains PD-1 expression on effector T cells to suppress T cell cytotoxicity, which causes immune escape and even affects the effectiveness of tumor immunotherapy [236–238]. Lactate in the tumor microenvironment also acts as an upstream molecule for the transcription factor NF-κB, and synergistically affect tumor angiogenesis [239].

Lipids are closely related to tumor immunity and TME. Lipids accumulated in the TME can regulate anti-tumor immunity [240, 241]. In TME, hypoglycemia and hypoxia promote fatty acid catabolism in $CD8^+$T cells and enhance its anti-tumor capacity [242]. Besides, obesity can also change the TME and the immune cell. High-fat diet changes lipids composition in TME, alters $CD8^+$T cell fatty acids uptake and reduces the function and number of $CD8^+$T cell. Finally harm the anti-tumor immunity [243]. Lipids also link TME and cell death together. For example, cholesterol in the TME upregulates CD36 expression in $CD8^+$T cell, leads to $CD8^+$T cell ferroptosis and inhibits its antitumor efficacy [244]. Tryptophan and CD8 + T cells also synergistically promote tumor cell apoptosis, thereby inhibiting tumor cell growth [245].

Transcription factors are involved in the regulation of a wide range of physiological activities, and there are many transcription factors with known functions that regulates metabolism, e.g., PPARs can participate in the regulation of lipid metabolism [246] and c-Myc can modulate glutamine metabolism [247]. c-Myc upregulates glutaminase (GLS) expression to promote glutamine catabolism [248], while glutamine deficiency induces myc-dependent apoptosis [249]. Transcription factors have an important role in the regulation of cell death. The first manifestation is in the promotion or inhibition of the cell death process. For example, the transcription factor Dlx2 suppresses canonical TGFβ signaling in tumor cells thereby inhibiting apoptosis [250]. Secondly, transcription factors shifts the type of cell death such as ATF3 converts hepatocyte apoptosis to necrotic apoptosis by regulating RIPK3 expression [251].

Table 1 Selected drugs or molecules associated with apoptosis in oncology research, their effects on apoptosis and targets of action

Cell death	Medicine	Inhibition or promotion	Target	References
Apoptosis	Smac/Diablo	Promotion	IAP	[269, 270]
Apoptosis	Sulforaphane	Promotion	Bax/Bak	[271]
Apoptosis	Cisatracurium	Promotion	lncRNA-p21	[272]
Apoptosis	Obatoclax	Promotion	Bcl-2, Survivin, Wnt/β-catenin pathway	[273, 274]
Apoptosis	NO.0449–0145	Promotion	APE1	[275]
Apoptosis	Curcumin	Promotion	Caspase8/9/3	[276, 277]
Apoptosis	Diosmetin	Promotion	STAT3/c-Myc pathway	[278]
Apoptosis	z-VDVAD-fmk, z-IETD-fmk	Inhibition	Caspase2/8	[279]
Apoptosis	Tauroursodeoxycholic acid	Inhibition	ER stress	[280]

Table 2 Selected drugs or molecules associated with necrosis in oncology research, the effects on necrosis and targets of action

Cell death	Medicine	Inhibition or promotion	Target	References
Necrosis	Tetrathiomolybdate	Promotion	Inhibit angiogenesis	[281]
Necrosis	Simvastatin, Metformin	Promotion	Ripk1, Ripk3	[282]
Necrosis	Melatonin	Promotion	Bcl2/Bax	[283]
Necrosis	CuZnSOD, MnSOD	Inhibition	Inhibit ROS generate	[284]

Table 3 Selected drugs or molecules associated with necroptosis in oncology research, their effects on necroptosis and targets of action

Cell death	Medicine	Inhibition or promotion	Target	References
Necroptosis	NO.0449–0145	Promotion	APE1	[275]
Necroptosis	CBL0137	Promotion	ZBP1	[86]
Necroptosis	BV6	Promotion	TNF-α	[285]
Necroptosis	Shikonin	Promotion	PKM2	[286]
Necroptosis	Necrostatin-1	Inhibition	RIP1	[287]
Necroptosis	NBC1	Inhibition	Hsp70	[288]

Table 4 Selected drugs or molecules associated with ferroptosis in oncology research, their effects on ferroptosis and targets of action

Cell death	Medicine	Inhibition or promotion	Target	References
Ferroptosis	Erastin	Promotion	System Xc^-	[98]
Ferroptosis	Brequinar	Promotion	DHODH	[289]
Ferroptosis	Nortriptyline hydrochloride	Promotion	RBMS1	[290]
Ferroptosis	Erianin	Promotion	Ca2+/CaM	[291]
Ferroptosis	RSL3	Promotion	GPX4, NF-κB	[292, 293]
Ferroptosis	Tagitinin C	Promotion	PERK-Nrf2-HO-1	[294]
Ferroptosis	Metformin	Promotion	SLC7A11	[295]
Ferroptosis	Dihydroartemisinin	Promotion	AMPK/mTOR/p70S6k	[296]
Ferroptosis	Elesclomol, copper	Promotion	ATP7A	[297]
Ferroptosis	Cetuximab	Promotion	NRF2/HO-1	[298]
Ferroptosis	EF24	Promotion	HMOX1	[299]
Ferroptosis	Flubendazole	Promotion	P53	[300]
Ferroptosis	Simvastatin	Promotion	HMGCR	[301]
Ferroptosis	Apatinib	Promotion	SREBP-1α, GSH	[302]
Ferroptosis	Ferrostatin-1, Liproxstatin-1	Inhibition	lipid peroxidation	[98, 303]
Ferroptosis	Dihydroartemisinin	Inhibition	PERK/ATF4/HSPA5	[304]

Targeting metabolism to induce cell death for tumor therapy

Compared to traditional chemotherapy and radiotherapy, cancer targeting therapy is more precise and has less side effects on the normal tissue [252–254]. Metabolism affects tumor development and plays a role in tumor therapy and prognosis. For example, the blockade of purine metabolism affects tumor cell proliferation and induces tumor death through inhibiting nucleic acid synthesis [255]. Or, we could also regulate tumor death by targeting intracellular carbon metabolism [256]. Meanwhile, current therapeutic approaches targeting cell death has made a good progress, proving that cell death can also be an effective tumor therapy target. Targeting cell death related-molecules such as Bcl-2 family proteins and NLRP3 effectively represses tumor growth [257, 258]. In addition, NLRP3, as an important inflammasome, is involved in immune checkpoint-related tumor immunotherapy [259]. We have summarized the drugs and molecules that can influence cell death in tumors (Tables 1, 2, 3, 4, 5 and 6). In addition to targeting metabolism and cell death respectively, many studies have now elucidated that targeting the interplay between them is a good strategy for cancer therapy [109, 260]. Taken together, with the in-depth study of the relationship between different metabolisms and cell death, we can treat tumors more effectively in the future.

Table 5 Selected drugs or molecules associated with pyroptosis in oncology research, their effects on pyroptosis and targets of action

Cell death	Medicine	Inhibition or promotion	Target	References
Pyroptosis	NO.0449 – 0145	Promotion	APE1A	[275]
Pyroptosis	Metformin	Promotion	AMPK/SIRT1/NF-κB	[305]
Pyroptosis	Paclitaxel, Cisplatin, Miltirone, Tetraarsenic hexoxide	Promotion	GSDME	[306–308]
Pyroptosis	α-KG	Promotion	DR6	[137]
Pyroptosis	Val-boroPro	Promotion	CARD8	[309]
Pyroptosis	Benzimidazoles	Promotion	NF-κB/NLRP3/GSDMD	[310]
Pyroptosis	Dihydroartemisinin	Promotion	AIM2/Caspase-3/DFNA5	[311]
Pyroptosis	Metformin	Promotion	FOXO3	[312]
Pyroptosis	Disulfiram, Cucurbitacin B	Inhibition	GSDMD	[313, 314]

Table 6 Selected drugs or molecules associated with autophagy in oncology research, their effects on autophagy and targets of action

Cell death	Medicine	Inhibition or promotion	Target	References
Autophagy	Carfilzomib, ONX 0912	Promotion	ATF4	[315]
Autophagy	Dihydromyricetin	Promotion	ROS/STAT3	[316]
Autophagy	Rapamycin, Latcripin-7 A, Metformin, RAD001	Promotion	mTOR	[317–320]
Autophagy	Narciclasine	Promotion	AMPK/ULK1	[321]
Autophagy	PX-866	Inhibition	PI3K	[322]

Conclusion

The wide spectrum of research on tumor metabolism has been developing for decades, including glucose metabolism, lipid metabolism, nucleotide metabolism, etc. For the cell death occurrence, the metabolic change-induced energy stress is one important reason. With the research in progress, knowledge on metabolic stress as an important influencing factor in tumors has been expanded. A variety of metabolism-related enzymes are related to tumor development and can be referenced for clinical therapy. Cell death is strongly linked to energy metabolism [261–263]. In particular, moreattentionhas been paidto the relationship between cell death and metabolism in tumors, as metabolism is found to be an effective way to mediate cell death [264–266]. Both energy production efficacy and capacities to produce the intermediates as signaling molecules for intracellular activities can be changed through following aspects, including affecting the enzymatic activities, regulating the levels of various key products from metabolic processes and the nutrients intake into cells [267, 268]. On the other hand, changes in metabolism also playsan important role in the induction of cell death in a variety of tumors [34, 37, 167]. These studies elucidate how cell death is regulated and affected by various metabolic pathways, and their roles during tumorigenesis and progression. Nevertheless, there are still many undiscovered regulatory relationships between metabolism and cell death that await for future studies.

Each of these cell death modes are regulated by cancer metabolism and can be involved in the regulation of tumorigenesis. Various metabolic processes promote or inhibit cell death not only through directly exerting stimuli that cause stress and cell death but also by affecting various important regulators of different cell death regulatory processes. In addition to these, the tumor microenvironment is also involved in the regulation of cell death by metabolism. Under certain circumstances, due to changes in intracellular metabolic profile and cell death, the tumor microenvironment will be affected accordingly. It indicates that it is feasible and effective to regulate tumorigenesis by modulating the tumor metabolism-cell death network. In the future studies, we may identify more targets associated with tumor metabolism to affect tumor cell death and discover more ways to regulate tumorigenesis and tumor therapy.

Abbreviations

PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
CTLA-4	cytotoxic T-lymphocyte antigen-4
GLUT4	glucose transporter 4
ISL1	Insulin gene enhancer protein 1
MC1R	melanocortin-1 receptor
EGFR	epidermal growth factor receptor
TCA cycle	tricarboxylic acid cycle
LKB1	liver kinase B1
RIPK1	Receptor-interacting protein kinase 1
mTOR	mammalian target of rapamycin
α-KG	α-ketoglutarate
GSDMC	gasdermin C
RCD	regulated cell death (RCD)
ICD	immunogenic cell death
DAMPs	damage-associated molecular patterns
IFNγ	interferon gamma
TME	tumor microenvironment
PI3K	phosphoinositide 3-kinase
HIF-1α	Hypoxia-inducible factor-1alpha
MCT1	monocarboxylate transporter 1
PPARs	peroxisome proliferator-activated receptors
GLS	glutaminase
LAT1	L-type amino acid transporter 1
OX-LDL	oxidized low-density lipoprotein
ACAT1	cholesterol acyltransferase 1
FASN	fatty acid synthase
NAMPT	icotinamide phosphoribosyltransferase

GLUT1	glucose transporter 1
ACLY	ATP citrate lyase
ACC1	Acetyl CoA carboxylase 1
α-KG	α-ketoglutarate
AKT	protein kinase B
F-1,6-2P	fructose-1,6-bisphosphate
TIGAR	TP53-induced glycolysis and apoptosis regulator
ROS	reactive oxygen species
ASCT2	alanine-serine-cysteine transporter 2
GLN	glutamine
BAX	bcl2 associated X protein
BAK	bcl2 antagonist/killer 1
TRADD	TNF receptor-associated death domain
PERK	protein kinase RNA-like endoplasmic reticulum kinase
mtDNA	mitochondrial DNA
ZBP1	Z-form nucleic acid binding protein 1
GLTP	glycolipid transfer protein
DMF	dimethyl fumarate
MLKL	mixed lineage kinase domain-like protein
DHA	docosahexaenoic acid
RIPK1	Receptor-interacting protein kinase 1
RIPK3	Receptor-interacting protein kinase 3
CARS	cysteinyl-tRNA synthetase
SREBP1	sterol-regulatory element binding protein 1
SREBP2	sterol-regulatory element binding protein 2
TF	transferrin
FABP1	fatty acid binding protein 1
PPARα	peroxisome proliferators-activated receptorα
MDM2	murine double minute2
MDMX	murine double minute
SCD1	stearoyl-CoA desaturase-1
CoQ10	coenzyme Q10
AMPK	adenosine 5′-monophosphate (AMP)-activated protein kinase
SLC7A11	solute carrier family 7 member 11
GPX4	glutathione peroxidase 4
LDLR	low-density lipoprotein receptor
FABP4	fatty acid binding protein 4
NLRP3	NOD-like receptor thermal protein domain associated protein 3
IL-1β	interleukin-1β
IL-18	interleukin-18
GSDMD	gasdermin D
DHA	docosahexaenoic acid
G-6-P	glucose-6-phosphate
F-6-P	fructose-6-phosphate
F-1,6-2P	fructose-1,6-bisphosphate
DHAP	dihydroxyacetone phosphate
PGAL	3-phosphoglyceraldehyde
3-PG	3-phosphoglycerate
2-PG	2-phosphoglycerate
PEP	Phosphoenolpyruvate
HK	hexokinase
PFK	phosphofructokinase
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
SIRT1	sirtuin 1
mTORC	mammalian target of rapamycin complex
TAK1	TGFβ-activated kinase 1
ULK1	Unc-51-like kinase 1
TF	transferrin

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Data availability
All data supporting Figs. 5 and 6 are available within the supplementary tables.

Declarations

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References

1. DeBerardinis RJ, Thompson CB. Cellular metabolism and disease: what do metabolic outliers teach us? Cell. 2012. https://doi.org/10.1016/j.cell.2012.02.032.
2. Musheshe N, et al. cAMP: from Long-Range Second Messenger to Nanodomain Signalling. Trends Pharmacol Sci. 2018. https://doi.org/10.1016/j.tips.2017.11.006.
3. Hemmrich K, et al. Nitric oxide and downstream second messenger cGMP and cAMP enhance adipogenesis in primary human preadipocytes. Cytotherapy. 2010. https://doi.org/10.3109/14653241003695042.
4. Choi HK, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med. 2004. https://doi.org/10.1056/NEJMoa035700.
5. Dalbeth N, et al. Gout. Nat Rev Dis Primers. 2019. https://doi.org/10.1038/s41572-019-0115-y.
6. DelNero P et al. Cancer metabolism gets physical. Science Translational Medicine. 2018;10.1126/scitranslmed.aaq1011.
7. Vaupel P, Multhoff G. Revisiting the Warburg effect: historical dogma versus current understanding. J Physiol. 2021. https://doi.org/10.1113/JP278810.
8. Green DR et al. Cell biology. Metabolic control of cell death. Science. 2014;10.1126/science.1250256.
9. Glick D, et al. Autophagy: cellular and molecular mechanisms. J Pathol. 2010. https://doi.org/10.1002/path.2697.
10. Riedl SJ, Salvesen GS. The apoptosome: signalling platform of cell death. Nat Rev Mol Cell Biol. 2007. https://doi.org/10.1038/nrm2153.
11. Munson MJ, Ganley IG. MTOR, PIK3C3, and autophagy: signaling the beginning from the end. Autophagy. 2015. https://doi.org/10.1080/15548627.2015.1106668.
12. Marsh T, Debnath J. Autophagy suppresses breast cancer metastasis by degrading NBR1. Autophagy. 2020. https://doi.org/10.1080/15548627.2020.1753001.
13. Xing Y, et al. Autophagy inhibition mediated by MCOLN1/TRPML1 suppresses cancer metastasis via regulating a ROS-driven TP53/p53 pathway. Autophagy. 2021. https://doi.org/10.1080/15548627.2021.2008752.
14. Strasser A, Vaux DL. Cell death in the origin and treatment of Cancer. Mol Cell. 2020. https://doi.org/10.1016/j.molcel.2020.05.014.

15. Tang R, et al. Ferroptosis, necroptosis, and pyroptosis in anticancer immunity. J Hematol Oncol. 2020. https://doi.org/10.1186/s13045-020-00946-7.
16. Wiig H, Swartz MA. Interstitial fluid and lymph formation and transport: physiological regulation and roles in inflammation and cancer. Physiol Rev. 2012. https://doi.org/10.1152/physrev.00037.2011.
17. Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. Pharmacol Ther. 2021. https://doi.org/10.1016/j.pharmthera.2020.107753.
18. Wang JX, et al. Lactic acid and an acidic Tumor Microenvironment suppress Anticancer Immunity. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21218363.
19. Qiu Y, et al. Activated T cell-derived exosomal PD-1 attenuates PD-L1-induced immune dysfunction in triple-negative breast cancer. Oncogene. 2021. https://doi.org/10.1038/s41388-021-01896-1.
20. Wei F, et al. PD-L1 promotes colorectal cancer stem cell expansion by activating HMGA1-dependent signaling pathways. Cancer Lett. 2019. https://doi.org/10.1016/j.canlet.2019.02.022.
21. Sun C et al. Regulation and Function of the PD-L1 Checkpoint. Immunity. 2018;10.1016/j.immuni.2018.03.014.
22. Yang Y, et al. Exosomal PD-L1 harbors active defense function to suppress T cell killing of breast cancer cells and promote tumor growth. Cell Res. 2018. https://doi.org/10.1038/s41422-018-0060-4.
23. Yang Y, et al. Palmitoylation stabilizes PD-L1 to promote breast tumor growth. Cell Res. 2019. https://doi.org/10.1038/s41422-018-0124-5.
24. Li CW et al. Glycosylation and stabilization of programmed death ligand-1 suppresses T-cell activity. Nat Commun. 2016;10.1038/ncomms12632.
25. Jiang X et al. Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. Mol Cancer. 2019;10.1186/s12943-018-0928-4.
26. Cerezo M et al. Translational control of tumor immune escape via the eIF4F-STAT1-PD-L1 axis in melanoma. Nat Med. 2018;10.1038/s41591-018-0217-1.
27. Casey SC et al. Cancer prevention and therapy through the modulation of the tumor microenvironment. Semin Cancer Biol. 2015;10.1016/j.semcancer.2015.02.007.
28. Wei G et al. Emerging immune checkpoints in the tumor microenvironment: Implications for cancer immunotherapy. Cancer Lett. 2021;10.1016/j.canlet.2021.04.021.
29. Sadeghi Rad H, et al. Understanding the tumor microenvironment for effective immunotherapy. Med Res Rev. 2021. https://doi.org/10.1002/med.21765.
30. Ketelut-Carneiro N, Fitzgerald KA. Apoptosis, pyroptosis, and Necroptosis-Oh my! The many ways a cell can die. J Mol Biol. 2022. https://doi.org/10.1016/j.jmb.2021.167378.
31. Sayers TJ. Targeting the extrinsic apoptosis signaling pathway for cancer therapy. Cancer Immunol Immunother 2011;10.1007/s00262-011-1008-4.
32. Singh R, et al. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. Nat Rev Mol Cell Biol. 2019. https://doi.org/10.1038/s41580-018-0089-8.
33. Zhang Z et al. DHHC9-mediated GLUT1 S-palmitoylation promotes glioblastoma glycolysis and tumorigenesis. Nat Commun. 2021;10.1038/s41467-021-26180-4.
34. Jensen PJ et al. GLUT1 deficiency links nutrient availability and apoptosis during embryonic development. J Biol Chem. 2006;10.1074/jbc.M601881200.
35. Wu XL et al. Effects of Glut1 gene silencing on proliferation, differentiation, and apoptosis of colorectal cancer cells by targeting the TGF-beta/PI3K-AKT-mTOR signaling pathway. J Cell Biochem. 2018;10.1002/jcb.26399.
36. Chen M et al. A p53-phosphoinositide signalosome regulates nuclear AKT activation. Nat Cell Biol. 2022;10.1038/s41556-022-00949-1.
37. Bensaad K et al. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell. 2006;10.1016/j.cell.2006.05.036.
38. Granchi C. ATP citrate lyase (ACLY) inhibitors: An anti-cancer strategy at the crossroads of glucose and lipid metabolism. Eur J Med Chem. 2018;10.1016/j.ejmech.2018.09.001.
39. Keenan MM et al. ACLY and ACC1 Regulate Hypoxia-Induced Apoptosis by Modulating ETV4 via alpha-ketoglutarate. PLoS Genet. 2015;10.1371/journal.pgen.1005599.
40. Gu L et al. The IKKbeta-USP30-ACLY Axis Controls Lipogenesis and Tumorigenesis. Hepatology. 2021;10.1002/hep.31249.
41. Icard P et al. ATP citrate lyase: A central metabolic enzyme in cancer. Cancer Lett. 2020;10.1016/j.canlet.2019.12.010.
42. Kiesel VA et al. Pyruvate carboxylase and cancer progression. Cancer Metab. 2021;10.1186/s40170-021-00256-7.
43. Bonfili L et al. Essential amino acid mixtures drive cancer cells to apoptosis through proteasome inhibition and autophagy activation. FEBS J. 2017;10.1111/febs.14081.
44. Uriarte M et al. Starvation-induced proteasome assemblies in the nucleus link amino acid supply to apoptosis. Nat Commun. 2021;10.1038/s41467-021-27306-4.
45. Fumarola C et al. Glutamine deprivation-mediated cell shrinkage induces ligand-independent CD95 receptor signaling and apoptosis. Cell Death Differ. 2001;10.1038/sj.cdd.4400902.
46. Chen L, Cui H. Targeting Glutamine Induces Apoptosis: A Cancer Therapy Approach. Int J Mol Sci 2015;10.3390/ijms160922830.
47. Jiang B et al. Filamentous GLS1 promotes ROS-induced apoptosis upon glutamine deprivation via insufficient asparagine synthesis. Mol Cell. 2022;10.1016/j.molcel.2022.03.016.
48. Chalecka M et al. P5C as an Interface of Proline Interconvertible Amino Acids and Its Role in Regulation of Cell Survival and Apoptosis. Int J Mol Sci. 2021;10.3390/ijms222111763.
49. Huynh TYL et al. Metformin Treatment or PRODH/POX-Knock out Similarly Induces Apoptosis by Reprograming of Amino Acid Metabolism, TCA, Urea Cycle and Pentose Phosphate Pathway in MCF-7 Breast Cancer Cells. Biomolecules. 2021;10.3390/biom11121888.
50. Markowicz-Piasecka M et al. Hemocompatible LAT1-inhibitor can induce apoptosis in cancer cells without affecting brain amino acid homeostasis. Apoptosis. 2020;10.1007/s10495-020-01603-7.
51. Montaser A et al. L-type amino acid transporter 1 (LAT1)-utilizing efflux transporter inhibitors can improve the brain uptake and apoptosis-inducing effects of vinblastine in cancer cells. Int J Pharm. 2020;10.1016/j.ijpharm.2020.119585.
52. Fu YM et al. Selective amino acid restriction targets mitochondria to induce apoptosis of androgen-independent prostate cancer cells. J Cell Physiol. 2006;10.1002/jcp.20766.
53. Dyntar D et al. Glucose and palmitic acid induce degeneration of myofibrils and modulate apoptosis in rat adult cardiomyocytes. Diabetes. 2001;10.2337/diabetes.50.9.2105.
54. Shen X et al. The effect of FFAR1 on pioglitazone-mediated attenuation of palmitic acid-induced oxidative stress and apoptosis in betaTC6 cells. Metabolism. 2014;10.1016/j.metabol.2013.11.003.
55. Chen L et al. G protein-coupled receptor 39 activation alleviates oxidized low-density lipoprotein-induced macrophage inflammatory response, lipid accumulation and apoptosis by inducing A20 expression. Bioengineered. 2021;10.1080/21655979.2021.1952917.
56. Wei Q et al. MiR-345-3p attenuates apoptosis and inflammation caused by oxidized low-density lipoprotein by targeting TRAF6 via TAK1/p38/NF-kB signaling in endothelial cells. Life Sci. 2020;10.1016/j.lfs.2019.117142.
57. Gu L et al. Stabilization of FASN by ACAT1-mediated GNPAT acetylation promotes lipid metabolism and hepatocarcinogenesis. Oncogene. 2020;10.1038/s41388-020-1156-0.
58. Hsieh PF, Cell suspension culture extract of Eriobotrya japonica attenuates growth and induces apoptosis in prostate cancer cells via targeting SREBP-1/FASN-driven metabolism and AR., Phytomedicine et al. 2021;10.1016/j.phymed.2021.153806.
59. Subedi A et al. Nicotinamide phosphoribosyltransferase inhibitors selectively induce apoptosis of AML stem cells by disrupting lipid homeostasis. Cell Stem Cell. 2021;10.1016/j.stem.2021.06.004.
60. Li YC et al. Elevated levels of cholesterol-rich lipid rafts in cancer cells are correlated with apoptosis sensitivity induced by cholesterol-depleting agents. Am J Pathol. 2006;10.2353/ajpath.2006.050959.
61. Balaban S et al. Heterogeneity of fatty acid metabolism in breast cancer cells underlies differential sensitivity to palmitate-induced apoptosis. Mol Oncol. 2018;10.1002/1878-0261.12368.
62. Matthews GM et al. Short-chain fatty acids induce apoptosis in colon cancer cells associated with changes to intracellular redox state and glucose metabolism. Chemotherapy. 2012;10.1159/000335672.
63. Judge A, Dodd MS, Metabolism. Essays Biochem. 2020;10:1042EBC20190041.
64. Wang R et al. Antiproliferative effect of mitochondria-targeting allobetulin 1,2,3-triazolium salt derivatives and their mechanism of inducing apoptosis of cancer cells. Eur J Med Chem. 2020;10.1016/j.ejmech.2020.112737.
65. Ryu H et al. The small molecule AU14022 promotes colorectal cancer cell death via p53-mediated G2/M-phase arrest and mitochondria-mediated apoptosis. J Cell Physiol. 2018;10.1002/jcp.26234.
66. Green DR, Llambi F. Cell Death Signaling. Cold Spring Harb Perspect Biol 2015;10.1101/cshperspect.a006080.
67. Samaratunga H et al. Granular necrosis: a distinctive form of cell death in malignant tumours. Pathology. 2020;10.1016/j.pathol.2020.06.002.

68. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nat Rev Cancer 2004;10.1038/nrc1478.
69. Leon-Annicchiarico CL et al. ATF4 mediates necrosis induced by glucose deprivation and apoptosis induced by 2-deoxyglucose in the same cells. FEBS J. 2015;10.1111/febs.13369.
70. Tian X et al. P53-independent partial restoration of the p53 pathway in tumors with mutated p53 through ATF4 transcriptional modulation by ERK1/2 and CDK9. Neoplasia. 2021;10.1016/j.neo.2021.01.004.
71. Horiguchi M et al. Rhythmic control of the ARF-MDM2 pathway by ATF4 underlies circadian accumulation of p53 in malignant cells. Cancer Res. 2013;10.1158/0008-5472.CAN-12-2492.
72. Khan MR et al. The p53-inducible long noncoding RNA TRINGS protects cancer cells from necrosis under glucose starvation. EMBO J. 2017;10.15252/embj.201696239.
73. Shao D et al. CHOP mediates XBP1S-induced renal mesangial cell necrosis following high glucose treatment. Eur J Pharmacol. 2015;10.1016/j.ejphar.2015.03.069.
74. Durham KK et al. High-density lipoprotein protects cardiomyocytes against necrosis induced by oxygen and glucose deprivation through SR-B1, PI3K, and AKT1 and 2. Biochem J. 2018;10.1042/BCJ20170703.
75. Hlatky L et al. Joint oxygen-glucose deprivation as the cause of necrosis in a tumor analog. J Cell Physiol. 1988;10.1002/jcp.1041340202.
76. Harwood SM et al. High glucose initiates calpain-induced necrosis before apoptosis in LLC-PK1 cells. Kidney International. 2007;10.1038/sj.ki.5002106.
77. McGinn S et al. High glucose and endothelial cell growth: novel effects independent of autocrine TGF-β1 and hyperosmolarity. American Journal of Physiology-Cell Physiology. 2003;10.1152/ajpcell.00466.2002.
78. Papo N et al. Suppression of human prostate tumor growth in mice by a cytolytic D-, L-amino Acid Peptide: membrane lysis, increased necrosis, and inhibition of prostate-specific antigen secretion. Cancer Res. 2004;10.1158/0008-5472.CAN-04-1438.
79. Gramaglia D et al. Apoptosis to necrosis switching downstream of apoptosome formation requires inhibition of both glycolysis and oxidative phosphorylation in a BCL-X(L)- and PKB/AKT-independent fashion. Cell Death Differ. 2004;10.1038/sj.cdd.4401326.
80. Lim S-C et al. Ethyl pyruvate induces necrosis-to-apoptosis switch and inhibits high mobility group box protein 1 release in A549 lung adenocarcinoma cells. International Journal of Molecular Medicine. 2007;10.3892/ijmm.20.2.187.
81. Kang. Hypoxia switches glucose depletion-induced necrosis to phosphoinositide 3-kinase/Akt-dependent apoptosis in A549 lung adenocarcinoma cells. International Journal of Oncology. 2009;10.3892/ijo_00000482.
82. Zong WX, Thompson CB. Necrotic death as a cell fate. Genes Dev. 2006;10.1101/gad.1376506.
83. Criddle DN et al. Calcium signalling and pancreatic cell death: apoptosis or necrosis? Cell Death Differ. 2007;10.1038/sj.cdd.4402150.
84. Wallach D et al. Programmed necrosis in inflammation: Toward identification of the effector molecules. Science. 2016;10.1126/science.aaf2154.
85. Kaczmarek A et al. Necroptosis: the release of damage-associated molecular patterns and its physiological relevance. Immunity. 2013;10.1016/j.immuni.2013.02.003.
86. Zhang T et al. ADAR1 masks the cancer immunotherapeutic promise of ZBP1-driven necroptosis. Nature. 2022;10.1038/s41586-022-04753-7.
87. Wang Y et al. Necroptosis regulates tumor repopulation after radiotherapy via RIP1/RIP3/MLKL/JNK/IL8 pathway. J Exp Clin Cancer Res. 2019;10.1186/s13046-019-1423-5.
88. Mishra SK et al. Upregulation of human glycolipid transfer protein (GLTP) induces necroptosis in colon carcinoma cells. Biochim Biophys Acta Mol Cell Biol Lipids. 2019;10.1016/j.bbalip.2018.11.002.
89. Baik JY et al. ZBP1 not RIPK1 mediates tumor necroptosis in breast cancer. Nat Commun. 2021;10.1038/s41467-021-23004-3.
90. Newell M et al. Docosahexaenoic acid enrichment of tumor phospholipid membranes increases tumor necroptosis in mice bearing triple negative breast cancer patient-derived xenografts. J Nutr Biochem. 2022;10.1016/j.jnutbio.2022.109018.
91. Pradhan AJ et al. Protein acylation by saturated very long chain fatty acids and endocytosis are involved in necroptosis. Cell Chem Biol. 2021;10.1016/j.chembiol.2021.03.012.
92. Xie X et al. Dimethyl fumarate induces necroptosis in colon cancer cells through GSH depletion/ROS increase/MAPKs activation pathway. Br J Pharmacol. 2015;10.1111/bph.13184.
93. Lee SB et al. The AMPK-Parkin axis negatively regulates necroptosis and tumorigenesis by inhibiting the necrosome. Nat Cell Biol. 2019;10.1038/s41556-019-0356-8.
94. Zhang DW et al. RIP3, an energy metabolism regulator that switches TNF-induced cell death from apoptosis to necrosis. Science. 2009;10.1126/science.1172308.
95. Ying L et al. The role of RIPK3-regulated cell death pathways and necroptosis in the pathogenesis of cardiac ischaemia-reperfusion injury. Acta Physiol (Oxf). 2021;10.1111/apha.13541.
96. Lin CC et al. RIPK3 upregulation confers robust proliferation and collateral cystine-dependence on breast cancer recurrence. Cell Death Differ. 2020;10.1038/s41418-020-0499-y.
97. Lee SY et al. Casein kinase-1gamma1 and 3 stimulate tumor necrosis factor-induced necroptosis through RIPK3. Cell Death Dis. 2019;10.1038/s41419-019-2146-4.
98. Dixon SJ et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;10.1016/j.cell.2012.03.042.
99. Parker JL et al. Molecular basis for redox control by the human cystine/glutamate antiporter system xc(). Nat Commun. 2021;10.1038/s41467-021-27414-1.
100. Li D, Li Y. The interaction between ferroptosis and lipid metabolism in cancer. Signal Transduct Target Ther 2020;10.1038/s41392-020-00216-5.
101. Liang D et al. Ferroptosis at the intersection of lipid metabolism and cellular signaling. Mol Cell. 2022;10.1016/j.molcel.2022.03.022.
102. Dierge E et al. Peroxidation of n-3 and n-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects. Cell Metab. 2021;10.1016/j.cmet.2021.05.016.
103. Ascenzi F et al. SCD1, autophagy and cancer: implications for therapy. J Exp Clin Cancer Res. 2021;10.1186/s13046-021-02067-6.
104. Tesfay L et al. Stearoyl-CoA Desaturase 1 Protects Ovarian Cancer Cells from Ferroptotic Cell Death. Cancer Res. 2019;10.1158/0008-5472.CAN-19-0369.
105. Ye Z et al. FBW7-NRA41-SCD1 axis synchronously regulates apoptosis and ferroptosis in pancreatic cancer cells. Redox Biol. 2021;10.1016/j.redox.2020.101807.
106. Luis G et al. Tumor resistance to ferroptosis driven by Stearoyl-CoA Desaturase-1 (SCD1) in cancer cells and Fatty Acid Biding Protein-4 (FABP4) in tumor microenvironment promote tumor recurrence. Redox Biol. 2021;10.1016/j.redox.2021.102006.
107. Wang C et al. Stearoyl-CoA desaturase 1 (SCD1) facilitates the growth and anti-ferroptosis of gastric cancer cells and predicts poor prognosis of gastric cancer. Aging (Albany NY). 2020;10.18632/aging.103598.
108. Yi J et al. Oncogenic activation of PI3K-AKT-mTOR signaling suppresses ferroptosis via SREBP-mediated lipogenesis. Proc Natl Acad Sci U S A. 2020;10.1073/pnas.2017152117.
109. Xuan Y et al. SCD1/FADS2 fatty acid desaturases equipoise lipid metabolic activity and redox-driven ferroptosis in ascites-derived ovarian cancer cells. Theranostics. 2022;10.7150/thno.70194.
110. Shao W, Espenshade PJ. Expanding roles for SREBP in metabolism. Cell Metab 2012;10.1016/j.cmet.2012.09.002.
111. Hong X et al. The Lipogenic Regulator SREBP2 Induces Transferrin in Circulating Melanoma Cells and Suppresses Ferroptosis. Cancer Discov. 2021;10.1158/2159–8290.CD-19-1500.
112. Pawlak M et al. Molecular mechanism of PPARalpha action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. J Hepatol. 2015;10.1016/j.jhep.2014.10.039.
113. Bougarne N et al. Molecular Actions of PPARalpha in Lipid Metabolism and Inflammation. Endocr Rev. 2018;10.1210/er.2018-00064.
114. Zhang N et al. N-glycosylation of CREBH improves lipid metabolism and attenuates lipotoxicity in NAFLD by modulating PPARalpha and SCD-1. FASEB J. 2020;10.1096/fj.202000836RR.
115. Venkatesh D et al. MDM2 and MDMX promote ferroptosis by PPARalpha-mediated lipid remodeling. Genes Dev. 2020;10.1101/gad.334219.119.
116. Wu J et al. Downregulation of PPARalpha mediates FABP1 expression, contributing to IgA nephropathy by stimulating ferroptosis in human mesangial cells. Int J Biol Sci. 2022;10.7150/ijbs.74675.
117. Yang WS et al. Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. Proc Natl Acad Sci U S A. 2016;10.1073/pnas.1603244113.
118. Liao P et al. CD8(+) T cells and fatty acids orchestrate tumor ferroptosis and immunity via ACSL4. Cancer Cell. 2022;10.1016/j.ccell.2022.02.003.
119. Ma Y et al. Energy metabolism as a regulator of ferroptosis. Cell Cycle. 2020;10.1080/15384101.2020.1838781.

120. Lee H et al. Energy-stress-mediated AMPK activation inhibits ferroptosis. Nat Cell Biol. 2020;10.1038/s41556-020-0461-8.
121. Badgley MA et al. Cysteine depletion induces pancreatic tumor ferroptosis in mice. Science. 2020;10.1126/science.aaw9872.
122. Koppula P et al. Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and cancer therapy. Protein Cell. 2021;10.1007/s13238-020-00789-5.
123. Sun Y et al. Glutathione depletion induces ferroptosis, autophagy, and premature cell senescence in retinal pigment epithelial cells. Cell Death Dis. 2018;10.1038/s41419-018-0794-4.
124. Niu B et al. Application of glutathione depletion in cancer therapy: Enhanced ROS-based therapy, ferroptosis, and chemotherapy. Biomaterials. 2021;10.1016/j.biomaterials.2021.121110.
125. Gao M et al. Glutaminolysis and Transferrin Regulate Ferroptosis. Mol Cell. 2015;10.1016/j.molcel.2015.06.011.
126. Dixon SJ et al. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife. 2014;10.7554/eLife.02523.
127. Hayano M et al. Loss of cysteinyl-tRNA synthetase (CARS) induces the transsulfuration pathway and inhibits ferroptosis induced by cystine deprivation. Cell Death Differ. 2016;10.1038/cdd.2015.93.
128. Liu T et al. The Deubiquitylase OTUB1 Mediates Ferroptosis via Stabilization of SLC7A11. Cancer Res. 2019;10.1158/0008-5472.CAN-18-3037.
129. Zhang Y et al. BAP1 links metabolic regulation of ferroptosis to tumour suppression. Nat Cell Biol. 2018;10.1038/s41556-018-0178-0.
130. Yang WS et al. Regulation of ferroptotic cancer cell death by GPX4. Cell. 2014;10.1016/j.cell.2013.12.010.
131. Seibt TM et al. Role of GPX4 in ferroptosis and its pharmacological implication. Free Radic Biol Med. 2019;10.1016/j.freeradbiomed.2018.09.014.
132. Zhang Y et al. mTORC1 couples cyst(e)ine availability with GPX4 protein synthesis and ferroptosis regulation. Nat Commun. 2021;10.1038/s41467-021-21841-w.
133. Yu P et al. Pyroptosis: mechanisms and diseases. Signal Transduct Target Ther. 2021;10.1038/s41392-021-00507-5.
134. Pizato N et al. Omega-3 docosahexaenoic acid induces pyroptosis cell death in triple-negative breast cancer cells. Sci Rep. 2018;10.1038/s41598-018-20422-0.
135. Huang Y et al. Inflammasome Activation and Pyroptosis via a Lipid-regulated SIRT1-p53-ASC Axis in Macrophages From Male Mice and Humans. Endocrinology. 2022;10.1210/endocr/bqac014.
136. Kang R et al. Lipid Peroxidation Drives Gasdermin D-Mediated Pyroptosis in Lethal Polymicrobial Sepsis. Cell Host Microbe. 2018;10.1016/j.chom.2018.05.009.
137. Zhang JY et al. The metabolite alpha-KG induces GSDMC-dependent pyroptosis through death receptor 6-activated caspase-8. Cell Res. 2021;10.1038/s41422-021-00506-9.
138. Sun R et al. Low-density lipoprotein receptor (LDLR) regulates NLRP3-mediated neuronal pyroptosis following cerebral ischemia/reperfusion injury. J Neuroinflammation. 2020;10.1186/s12974-020-01988-x.
139. Sun Z et al. Inhibition of SGLT1 protects against glycemic variability-induced cardiac damage and pyroptosis of cardiomyocytes in diabetic mice. Life Sci. 2021;10.1016/j.lfs.2021.119116.
140. Kim SR et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. Nat Commun. 2020;10.1038/s41467-020-15983-6.
141. Wen H et al. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol. 2011;10.1038/ni.2022.
142. Ahechu P et al. NLRP3 Inflammasome: A Possible Link Between Obesity-Associated Low-Grade Chronic Inflammation and Colorectal Cancer Development. Front Immunol. 2018;10.3389/fimmu.2018.02918.
143. Tsvetkov P et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. Science. 2022;10.1126/science.abf0529.
144. Zheng P et al. Elesclomol: a copper ionophore targeting mitochondrial metabolism for cancer therapy. J Exp Clin Cancer Res. 2022;10.1186/s13046-022-02485-0.
145. Sheftel AD et al. Humans possess two mitochondrial ferredoxins, Fdx1 and Fdx2, with distinct roles in steroidogenesis, heme, and Fe/S cluster biosynthesis. Proceedings of the National Academy of Sciences. 2010;10.1073/pnas.1004250107.
146. Tang D et al. Cuproptosis: a copper-triggered modality of mitochondrial cell death. Cell Research. 2022;10.1038/s41422-022-00653-7.
147. Xue Q et al. Copper metabolism in cell death and autophagy. Autophagy. 2023;10.1080/15548627.2023.2200554.
148. Mo X et al. A novel cuproptosis-related prognostic lncRNA signature and lncRNA MIR31HG/miR-193a-3p/TNFRSF21 regulatory axis in lung adenocarcinoma. Front Oncol. 2022;10.3389/fonc.2022.927706.
149. Yang M et al. A novel signature to guide osteosarcoma prognosis and immune microenvironment: Cuproptosis-related lncRNA. Front Immunol. 2022;10.3389/fimmu.2022.919231.
150. Zhang Z et al. Cuproptosis-Related Risk Score Predicts Prognosis and Characterizes the Tumor Microenvironment in Hepatocellular Carcinoma. Front Immunol. 2022;10.3389/fimmu.2022.925618.
151. Ji ZH et al. Molecular Subtyping Based on Cuproptosis-Related Genes and Characterization of Tumor Microenvironment Infiltration in Kidney Renal Clear Cell Carcinoma. Front Oncol. 2022;10.3389/fonc.2022.919083.
152. Lv H et al. Comprehensive Analysis of Cuproptosis-Related Genes in Immune Infiltration and Prognosis in Melanoma. Front Pharmacol. 2022;10.3389/fphar.2022.930041.
153. Shi L, Tu BP. Acetyl-CoA and the regulation of metabolism: mechanisms and consequences. Curr Opin Cell Biol 2015;10.1016/j.ceb.2015.02.003.
154. Boya P et al. Emerging regulation and functions of autophagy. Nat Cell Biol. 2013;10.1038/ncb2788.
155. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell. 2008;10.1016/j.cell.2007.12.018.
156. Lu Q et al. Akt inhibition attenuates rasfonin-induced autophagy and apoptosis through the glycolytic pathway in renal cancer cells. Cell Death Dis. 2015;10.1038/cddis.2015.344.
157. Roberts DJ, Miyamoto S. Hexokinase II integrates energy metabolism and cellular protection: Akting on mitochondria and TORCing to autophagy. Cell Death Differ 2015;10.1038/cdd.2014.173.
158. Roberts DJ et al. Hexokinase-II positively regulates glucose starvation-induced autophagy through TORC1 inhibition. Mol Cell. 2014;10.1016/j.molcel.2013.12.019.
159. Lamming DW et al. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. Science. 2012;10.1126/science.1215135.
160. Luo L et al. BCAT1 decreases the sensitivity of cancer cells to cisplatin by regulating mTOR-mediated autophagy via branched-chain amino acid metabolism. Cell Death Dis. 2021;10.1038/s41419-021-03456-7.
161. Tan J et al. JMJD2B-induced amino acid alterations enhance the survival of colorectal cancer cells under glucose-deprivation via autophagy. Theranostics. 2020;10.7150/thno.38087.
162. Nowosad A et al. p27 controls Ragulator and mTOR activity in amino acid-deprived cells to regulate the autophagy-lysosomal pathway and coordinate cell cycle and cell growth. Nat Cell Biol. 2020;10.1038/s41556-020-0554-4.
163. Saha S et al. The tumor-suppressive long noncoding RNA DRAIC inhibits protein translation and induces autophagy by activating AMPK. J Cell Sci. 2021;10.1242/jcs.259306.
164. Karabiyik C et al. Glucose starvation induces autophagy via ULK1-mediated activation of PIKfyve in an AMPK-dependent manner. Dev Cell. 2021;10.1016/j.devcel.2021.05.010.
165. Egan DF et al. Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. Science. 2011;10.1126/science.1196371.
166. Chung SJ et al. ADIPOQ/adiponectin induces cytotoxic autophagy in breast cancer cells through STK11/LKB1-mediated activation of the AMPK-ULK1 axis. Autophagy. 2017;10.1080/15548627.2017.1332565.
167. Chang C et al. AMPK-Dependent Phosphorylation of GAPDH Triggers Sirt1 Activation and Is Necessary for Autophagy upon Glucose Starvation. Mol Cell. 2015;10.1016/j.molcel.2015.10.037.
168. Qian X et al. Phosphoglycerate Kinase 1 Phosphorylates Beclin1 to Induce Autophagy. Mol Cell. 2017;10.1016/j.molcel.2017.01.027.
169. Mukha A et al. Targeting glutamine metabolism and autophagy: the combination for prostate cancer radiosensitization. Autophagy. 2021;10.1080/15548627.2021.1962682.
170. Eng CH et al. Ammonia derived from glutaminolysis is a diffusible regulator of autophagy. Sci Signal. 2010;10.1126/scisignal.2000911.
171. Xia XJ et al. Autophagy mediated by arginine depletion activation of the nutrient sensor GCN2 contributes to interferon-gamma-induced malignant transformation of primary bovine mammary epithelial cells. Cell Death Discov. 2016;10.1038/cddiscovery.2015.65.

172. Garcia-Navas R et al. Depletion of L-arginine induces autophagy as a cytoprotective response to endoplasmic reticulum stress in human T lymphocytes. Autophagy. 2012;10.4161/auto.21315.
173. Zhang X et al. Nitric oxide inhibits autophagy and promotes apoptosis in hepatocellular carcinoma. Cancer Sci. 2019;10.1111/cas.13945.
174. Stacchiotti A, Corsetti G. Natural Compounds and Autophagy: Allies Against Neurodegeneration. Front Cell Dev Biol 2020;10.3389/fcell.2020.555409.
175. Sivangala Thandi R et al. Ornithine-A urea cycle metabolite enhances autophagy and controls Mycobacterium tuberculosis infection. Nat Commun. 2020;10.1038/s41467-020-17310-5.
176. Halama A et al. Accelerated lipid catabolism and autophagy are cancer survival mechanisms under inhibited glutaminolysis. Cancer Lett. 2018;10.1016/j.canlet.2018.05.017.
177. Singh R et al. Autophagy regulates lipid metabolism. Nature. 2009;10.1038/nature07976.
178. Giampietri C et al. Lipid Storage and Autophagy in Melanoma Cancer Cells. Int J Mol Sci. 2017;10.3390/ijms18061271.
179. Inokuchi-Shimizu S et al. TAK1-mediated autophagy and fatty acid oxidation prevent hepatosteatosis and tumorigenesis. J Clin Invest. 2014;10.1172/JCI74068.
180. Seok JK et al. Oxidized Phospholipids in Tumor Microenvironment Stimulate Tumor Metastasis via Regulation of Autophagy. Cells. 2021;10.3390/cells10030558.
181. Rios-Marco P et al. Alkylphospholipids deregulate cholesterol metabolism and induce cell-cycle arrest and autophagy in U-87 MG glioblastoma cells. Biochim Biophys Acta. 2013;10.1016/j.bbalip.2013.05.004.
182. Mece O et al. Lipid droplet degradation by autophagy connects mitochondria metabolism to Prox1-driven expression of lymphatic genes and lymphangiogenesis. Nat Commun. 2022;10.1038/s41467-022-30490-6.
183. Guo JY et al. Autophagy suppresses progression of K-ras-induced lung tumors to oncocytomas and maintains lipid homeostasis. Genes Dev. 2013;10.1101/gad.219642.113.
184. He Z et al. p73 regulates autophagy and hepatocellular lipid metabolism through a transcriptional activation of the ATG5 gene. Cell Death Differ. 2013;10.1038/cdd.2013.104.
185. Karvela M et al. ATG7 regulates energy metabolism, differentiation and survival of Philadelphia-chromosome-positive cells. Autophagy. 2016;10.1080/15548627.2016.1162359.
186. Saito T et al. Autophagy regulates lipid metabolism through selective turnover of NCoR1. Nat Commun. 2019;10.1038/s41467-019-08829-3.
187. Kessel DH et al. ATG7 deficiency suppresses apoptosis and cell death induced by lysosomal photodamage. Autophagy. 2012;10.4161/auto.20792.
188. Hay N. Reprogramming glucose metabolism in cancer: can it be exploited for cancer therapy? Nature Reviews Cancer. 2016;10.1038/nrc.2016.77.
189. Guo T et al. Insulin gene enhancer protein 1 mediates glycolysis and tumorigenesis of gastric cancer through regulating glucose transporter 4. Cancer Communications. 2021;10.1002/cac2.12141.
190. Ancey P-B et al. GLUT1 Expression in Tumor-Associated Neutrophils Promotes Lung Cancer Growth and Resistance to Radiotherapy. Cancer Research. 2021;10.1158/0008-5472.Can-20-2870.
191. Li Y et al. Homeostasis Imbalance of YY2 and YY1 Promotes Tumor Growth by Manipulating Ferroptosis. Advanced Science. 2022;10.1002/advs.202104836.
192. Ma L et al. The m6A reader YTHDC2 inhibits lung adenocarcinoma tumorigenesis by suppressing SLC7A11-dependent antioxidant function. Redox Biology. 2021;10.1016/j.redox.2020.101801.
193. Duan F et al. O -GlcNAcylation of RACK1 promotes hepatocellular carcinogenesis. Journal of Hepatology. 2018;10.1016/j.jhep.2018.02.003.
194. Cheng C et al. Glucose-Mediated N-glycosylation of SCAP Is Essential for SREBP-1 Activation and Tumor Growth. Cancer Cell. 2015;10.1016/j.ccell.2015.09.021.
195. Liu Y et al. N-glycosylation stabilizes MerTK and promotes hepatocellular carcinoma tumor growth. Redox Biology. 2022;10.1016/j.redox.2022.102366.
196. Kharbanda A et al. Blocking EGFR palmitoylation suppresses PI3K signaling and mutant KRAS lung tumorigenesis. Science Signaling. 2020;10.1126/scisignal.aax2364.
197. Kadry YA et al. Regulation of EGFR signalling by palmitoylation and its role in tumorigenesis. Open Biology. 2021;10.1098/rsob.210033.
198. Chen S et al. Palmitoylation-dependent activation of MC1R prevents melanomagenesis. Nature. 2017;10.1038/nature23887.
199. Yang J et al. A Positive Feedback Loop between Inactive VHL-Triggered Histone Lactylation and PDGFRβ Signaling Drives Clear Cell Renal Cell Carcinoma Progression. International Journal of Biological Sciences. 2022;10.7150/ijbs.73398.
200. Chen L et al. Lactate-Lactylation Hands between Metabolic Reprogramming and Immunosuppression. International Journal of Molecular Sciences. 2022;10.3390/ijms231911943.
201. Yu J et al. Histone lactylation drives oncogenesis by facilitating m6A reader protein YTHDF2 expression in ocular melanoma. Genome Biology. 2021;10.1186/s13059-021-02308-z.
202. Li F et al. NADP+-IDH Mutations Promote Hypersuccinylation that Impairs Mitochondria Respiration and Induces Apoptosis Resistance. Molecular Cell. 2015;10.1016/j.molcel.2015.10.017.
203. Xie J et al. Cuproptosis: mechanisms and links with cancers. Molecular Cancer. 2023;10.1186/s12943-023-01732-y.
204. Bandmann O et al. Wilson's disease and other neurological copper disorders. The Lancet Neurology. 2015;10.1016/s1474-4422(14)70190-5.
205. Cui L et al. Mitochondrial copper depletion suppresses triple-negative breast cancer in mice. Nature Biotechnology. 2020;10.1038/s41587-020-0707-9.
206. Stockwell BR et al. Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease. Cell. 2017;10.1016/j.cell.2017.09.021.
207. Mihaylova MM, Shaw RJ. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nat Cell Biol 2011;10.1038/ncb2329.
208. Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol 2018;10.1038/nrm.2017.95.
209. Zhang T et al. Metabolic orchestration of cell death by AMPK-mediated phosphorylation of RIPK1. Science. 2023;10.1126/science.abn1725.
210. Guo H et al. Induction of autophagy via the ROS-dependent AMPK-mTOR pathway protects copper-induced spermatogenesis disorder. Redox Biology. 2022;10.1016/j.redox.2021.102227.
211. Kim J et al. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nature Cell Biology. 2011;10.1038/ncb2152.
212. Liu W et al. TRIM22 inhibits osteosarcoma progression through destabilizing NRF2 and thus activation of ROS/AMPK/mTOR/autophagy signaling. Redox Biology. 2022;10.1016/j.redox.2022.102344.
213. Wei Q et al. Maslinic Acid Inhibits Colon Tumorigenesis by the AMPK–mTOR Signaling Pathway. Journal of Agricultural and Food Chemistry. 2019;10.1021/acs.jafc.9b00170.
214. Wang X et al. HKDC1 promotes the tumorigenesis and glycolysis in lung adenocarcinoma via regulating AMPK/mTOR signaling pathway. Cancer Cell International. 2020;10.1186/s12935-020-01539-7.
215. Huang J et al. Ginseng polysaccharides alter the gut microbiota and kynurenine/tryptophan ratio, potentiating the antitumour effect of antiprogrammed cell death 1/programmed cell death ligand 1 (anti-PD-1/PD-L1) immunotherapy. Gut. 2022;10.1136/gutjnl-2020-321031.
216. Lee K-H, Kang T-B. The Molecular Links between Cell Death and Inflammasome. Cells 2019;10.3390/cells8091057.
217. Medina CB et al. Metabolites released from apoptotic cells act as tissue messengers. Nature. 2020;10.1038/s41586-020-2121-3.
218. Du T et al. Pyroptosis, metabolism, and tumor immune microenvironment. Clin Transl Med. 2021;10.1002/ctm2.492.
219. Erkes DA et al. Mutant BRAF and MEK Inhibitors Regulate the Tumor Immune Microenvironment via Pyroptosis. Cancer Discov. 2020;10.1158/2159–8290.CD-19-0672.
220. Krysko DV et al. Immunogenic cell death and DAMPs in cancer therapy. Nature Reviews Cancer. 2012;10.1038/nrc3380.
221. Galluzzi L et al. Immunogenic cell death in cancer and infectious disease. Nature Reviews Immunology. 2016;10.1038/nri.2016.107.
222. Obeid M et al. Calreticulin exposure dictates the immunogenicity of cancer cell death. Nature Medicine. 2006;10.1038/nm1523.
223. Wang W et al. CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy. Nature. 2019;10.1038/s41586-019-1170-y.
224. Efimova I et al. Vaccination with early ferroptotic cancer cells induces efficient antitumor immunity. Journal for ImmunoTherapy of Cancer. 2020;10.1136/jitc-2020-001369.
225. Tong X et al. Targeting cell death pathways for cancer therapy: recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. Journal of Hematology & Oncology. 2022;10.1186/s13045-022-01392-3.
226. Qin Y et al. Cuproptosis correlates with immunosuppressive tumor microenvironment based on pan-cancer multiomics and single-cell sequencing analysis. Molecular Cancer. 2023;10.1186/s12943-023-01752-8.
227. Jin Y et al. CRMP2 derived from cancer associated fibroblasts facilitates progression of ovarian cancer via HIF-1α-glycolysis signaling pathway. Cell Death & Disease. 2022;10.1038/s41419-022-05129-5.

228. Wang Z-H et al. Lactate in the tumour microenvironment: From immune modulation to therapy. EBioMedicine. 2021;10.1016/j.ebiom.2021.103627.
229. Rabiee S et al. Autophagic, apoptotic, and necrotic cancer cell fates triggered by acidic pH microenvironment. J Cell Physiol. 2019;10.1002/jcp.27876.
230. Zhang A et al. Lactate-induced M2 polarization of tumor-associated macrophages promotes the invasion of pituitary adenoma by secreting CCL17. Theranostics. 2021;10.7150/thno.53749.
231. Vitale I et al. Macrophages and Metabolism in the Tumor Microenvironment. Cell Metab. 2019;10.1016/j.cmet.2019.06.001.
232. Chen D et al. Metabolic regulatory crosstalk between tumor microenvironment and tumor-associated macrophages. Theranostics. 2021;10.7150/thno.51777.
233. Sacco A et al. Iron Metabolism in the Tumor Microenvironment-Implications for Anti-Cancer Immune Response. Cells. 2021;10.3390/cells10020303.
234. Fischer K et al. Inhibitory effect of tumor cell–derived lactic acid on human T cells. Blood. 2007;10.1182/blood-2006-07-035972.
235. Watson MJ et al. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. Nature. 2021;10.1038/s41586-020-03045-2.
236. Kumagai S et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. Cancer Cell. 2022;10.1016/j.ccell.2022.01.001.
237. Deng H et al. Tumor-derived lactate inhibit the efficacy of lenvatinib through regulating PD-L1 expression on neutrophil in hepatocellular carcinoma. Journal for ImmunoTherapy of Cancer. 2021;10.1136/jitc-2020-002305.
238. Lim JX et al. Programmed cell death-1 receptor-mediated regulation of Tbet. +. NK1.1. –. innate lymphoid cells within the tumor microenvironment. Proceedings of the National Academy of Sciences. 2023;10.1073/pnas.2216587120.
239. Végran F et al. Lactate Influx through the Endothelial Cell Monocarboxylate Transporter MCT1 Supports an NF-κB/IL-8 Pathway that Drives Tumor Angiogenesis. Cancer Research. 2011;10.1158/0008-5472.Can-10-2828.
240. Manzo T et al. Accumulation of long-chain fatty acids in the tumor microenvironment drives dysfunction in intrapancreatic CD8 + T cells. Journal of Experimental Medicine. 2020;10.1084/jem.20191920.
241. Yang K et al. The role of lipid metabolic reprogramming in tumor microenvironment. Theranostics. 2023;10.7150/thno.82920.
242. Zhang Y et al. Enhancing CD8 + T Cell Fatty Acid Catabolism within a Metabolically Challenging Tumor Microenvironment Increases the Efficacy of Melanoma Immunotherapy. Cancer Cell. 2017;10.1016/j.ccell.2017.08.004.
243. Ringel AE et al. Obesity Shapes Metabolism in the Tumor Microenvironment to Suppress Anti-Tumor Immunity. Cell. 2020;10.1016/j.cell.2020.11.009.
244. Ma X et al. CD36-mediated ferroptosis dampens intratumoral CD8 + T cell effector function and impairs their antitumor ability. Cell Metabolism. 2021;10.1016/j.cmet.2021.02.015.
245. Qin R et al. Tryptophan potentiates CD8(+) T cells against cancer cells by TRIP12 tryptophanylation and surface PD-1 downregulation. J Immunother Cancer. 2021;10.1136/jitc-2021-002840.
246. Gross B et al. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. Nature Reviews Endocrinology. 2016;10.1038/nrendo.2016.135.
247. Ganguly K et al. Mucin 5AC Serves as the Nexus for β-Catenin/c-Myc Interplay to Promote Glutamine Dependency During Pancreatic Cancer Chemoresistance. Gastroenterology. 2022;10.1053/j.gastro.2021.09.017.
248. Gao P et al. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. Nature. 2009;10.1038/nature07823.
249. Yuneva M et al. Deficiency in glutamine but not glucose induces MYC-dependent apoptosis in human cells. The Journal of Cell Biology. 2007;10.1083/jcb.200703099.
250. Yilmaz M et al. Transcription factor Dlx2 protects from TGFβ-induced cell-cycle arrest and apoptosis. The EMBO Journal. 2011;10.1038/emboj.2011.319.
251. Inaba Y et al. The transcription factor ATF3 switches cell death from apoptosis to necroptosis in hepatic steatosis in male mice. Nature Communications. 2023;10.1038/s41467-023-35804-w.
252. van den Bulk J et al. Cancer immunotherapy: broadening the scope of targetable tumours. Open Biol. 2018;10.1098/rsob.180037.
253. Mantovani A et al. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017;10.1038/nrclinonc.2016.217.
254. Chang L et al. Targeting pan-essential genes in cancer: Challenges and opportunities. Cancer Cell. 2021;10.1016/j.ccell.2020.12.008.
255. Yin J et al. Potential Mechanisms Connecting Purine Metabolism and Cancer Therapy. Front Immunol. 2018;10.3389/fimmu.2018.01697.
256. Ser Z et al. Targeting One Carbon Metabolism with an Antimetabolite Disrupts Pyrimidine Homeostasis and Induces Nucleotide Overflow. Cell Reports. 2016;10.1016/j.celrep.2016.05.035.
257. Thomas S et al. Targeting the Bcl-2 family for cancer therapy. Expert Opin Ther Targets. 2013;10.1517/14728222.2013.733001.
258. Tengesdal IW et al. Targeting tumor-derived NLRP3 reduces melanoma progression by limiting MDSCs expansion. Proc Natl Acad Sci U S A. 2021;10.1073/pnas.2000915118.
259. Theivanthiran B et al. A tumor-intrinsic PD-L1/NLRP3 inflammasome signaling pathway drives resistance to anti-PD-1 immunotherapy. J Clin Invest. 2020;10.1172/JCI133055.
260. Carbone M, Melino G. Lipid metabolism offers anticancer treatment by regulating ferroptosis. Cell Death Differ 2019;10.1038/s41418-019-0418-2.
261. Chen HT et al. Crosstalk between autophagy and epithelial-mesenchymal transition and its application in cancer therapy. Mol Cancer. 2019;10.1186/s12943-019-1030-2.
262. White E et al. Autophagy, metabolism, and Cancer. Clin Cancer Res 2015;10.1158/1078 – 0432.CCR-15-0490.
263. Levy JMM et al. Targeting autophagy in cancer. Nat Rev Cancer. 2017;10.1038/nrc.2017.53.
264. Andersen JL, Kornbluth S. The tangled circuitry of metabolism and apoptosis. Mol Cell. 2013;10.1016/j.molcel.2012.12.026.
265. Kim KH, Lee MS. Autophagy–a key player in cellular and body metabolism. Nat Rev Endocrinol 2014;10.1038/nrendo.2014.35.
266. Zheng J, Conrad M. The Metabolic Underpinnings of Ferroptosis. Cell Metab 2020;10.1016/j.cmet.2020.10.011.
267. Mulukutla BC et al. Regulation of Glucose Metabolism - A Perspective From Cell Bioprocessing. Trends Biotechnol. 2016;10.1016/j.tibtech.2016.04.012.
268. Ye J, Medzhitov R. Control strategies in systemic metabolism. Nat Metab 2019;10.1038/s42255-019-0118-8.
269. Verhagen AM et al. Identification of DIABLO, a Mammalian Protein that Promotes Apoptosis by Binding to and Antagonizing IAP Proteins. Cell. 2000;10.1016/s0092-8674(00)00009-x.
270. Du C et al. Smac, a Mitochondrial Protein that Promotes Cytochrome c–Dependent Caspase Activation by Eliminating IAP Inhibition. Cell. 2000;10.1016/s0092-8674(00)00008–8.
271. Choi S, Singh SV. Bax and Bak are required for apoptosis induction by sulforaphane, a cruciferous vegetable-derived cancer chemopreventive agent. Cancer Res 2005;10.1158/0008-5472.CAN-04-3616.
272. Zhu D et al. Cisatracurium inhibits the growth and induces apoptosis of ovarian cancer cells by promoting lincRNA-p21. Bioengineered. 2021;10.1080/21655979.2021.1916271.
273. Chiappori A et al. Obatoclax Mesylate, a Pan–Bcl-2 Inhibitor, in Combination with Docetaxel in a Phase 1/2 Trial in Relapsed Non–Small-Cell Lung Cancer. Journal of Thoracic Oncology. 2014;10.1097/jto.0000000000000027.
274. Or CR et al. Obatoclax, a Pan-BCL-2 Inhibitor, Downregulates Survivin to Induce Apoptosis in Human Colorectal Carcinoma Cells Via Suppressing WNT/beta-catenin Signaling. Int J Mol Sci. 2020;10.3390/ijms21051773.
275. Long K et al. Small-molecule inhibition of APE1 induces apoptosis, pyroptosis, and necroptosis in non-small cell lung cancer. Cell Death Dis. 2021;10.1038/s41419-021-03804-7.
276. Wu L-Y et al. Curcumin Attenuates Adipogenesis by Inducing Preadipocyte Apoptosis and Inhibiting Adipocyte Differentiation. Nutrients. 2019;10.3390/nu11102307.
277. Zhou C et al. Curcumin inhibits AP-2gamma-induced apoptosis in the human malignant testicular germ cells in vitro. Acta Pharmacol Sin. 2013;10.1038/aps.2013.38.
278. Ning R et al. Diosmetin inhibits cell proliferation and promotes apoptosis through STAT3/c-Myc signaling pathway in human osteosarcoma cells. Biol Res. 2021;10.1186/s40659-021-00363-1.
279. Kim BM, Hong SH. Sequential caspase-2 and caspase-8 activation is essential for saikosaponin a-induced apoptosis of human colon carcinoma cell lines. Apoptosis 2011;10.1007/s10495-010-0557-x.
280. Vandewynckel YP et al. Tauroursodeoxycholic acid dampens oncogenic apoptosis induced by endoplasmic reticulum stress during hepatocarcinogen exposure. Oncotarget. 2015;10.18632/oncotarget.4377.
281. Hassouneh B et al. Tetrathiomolybdate promotes tumor necrosis and prevents distant metastases by suppressing angiogenesis in head and neck cancer. Mol Cancer Ther. 2007;10.1158/1535–7163.MCT-06-0524.
282. Babcook MA et al. Combination simvastatin and metformin induces G1-phase cell cycle arrest and Ripk1- and Ripk3-dependent necrosis in C4-2B

osseous metastatic castration-resistant prostate cancer cells. Cell Death Dis. 2014;10.1038/cddis.2014.500.
283. Xu C et al. Melatonin is involved in the apoptosis and necrosis of pancreatic cancer cell line SW-1990 via modulating of Bcl-2/Bax balance. Biomed Pharmacother. 2013;10.1016/j.biopha.2012.10.005.
284. Lee SY et al. CuZnSOD and MnSOD inhibit metabolic stress-induced necrosis and multicellular tumour spheroid growth. Int J Oncol. 2010;10.3892/ijo_00000667.
285. Hannes S et al. Smac mimetic triggers necroptosis in pancreatic carcinoma cells when caspase activation is blocked. Cancer Lett. 2016;10.1016/j.canlet.2016.05.036.
286. Wang Y et al. PKM2 Inhibitor Shikonin Overcomes the Cisplatin Resistance in Bladder Cancer by Inducing Necroptosis. Int J Biol Sci. 2018;10.7150/ijbs.27854.
287. Cao L, Mu W. Necrostatin-1 and necroptosis inhibition: Pathophysiology and therapeutic implications. Pharmacol Res 2021;10.1016/j.phrs.2020.105297.
288. Johnston AN et al. Necroptosis-blocking compound NBC1 targets heat shock protein 70 to inhibit MLKL polymerization and necroptosis. Proc Natl Acad Sci U S A. 2020;10.1073/pnas.1916503117.
289. Mao C et al. DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. Nature. 2021;10.1038/s41586-021-03539-7.
290. Zhang W et al. RBMS1 regulates lung cancer ferroptosis through translational control of SLC7A11. J Clin Invest. 2021;10.1172/JCI152067.
291. Chen P et al. Erianin, a novel dibenzyl compound in Dendrobium extract, inhibits lung cancer cell growth and migration via calcium/calmodulin-dependent ferroptosis. Signal Transduct Target Ther. 2020;10.1038/s41392-020-0149-3.
292. Sui X et al. RSL3 Drives Ferroptosis Through GPX4 Inactivation and ROS Production in Colorectal Cancer. Front Pharmacol. 2018;10.3389/fphar.2018.01371.
293. Li S et al. RSL3 Drives Ferroptosis through NF-kappaB Pathway Activation and GPX4 Depletion in Glioblastoma. Oxid Med Cell Longev. 2021;10.1155/2021/2915019.
294. Wei R et al. Tagitinin C induces ferroptosis through PERK-Nrf2-HO-1 signaling pathway in colorectal cancer cells. Int J Biol Sci. 2021;10.7150/ijbs.59404.
295. Yang J et al. Metformin induces Ferroptosis by inhibiting UFMylation of SLC7A11 in breast cancer. J Exp Clin Cancer Res. 2021;10.1186/s13046-021-02012-7.
296. Du J et al. DHA inhibits proliferation and induces ferroptosis of leukemia cells through autophagy dependent degradation of ferritin. Free Radic Biol Med. 2019;10.1016/j.freeradbiomed.2018.12.011.
297. Gao W et al. Elesclomol induces copper-dependent ferroptosis in colorectal cancer cells via degradation of ATP7A. Mol Oncol. 2021;10.1002/1878-0261.13079.
298. Yang J et al. Cetuximab promotes RSL3-induced ferroptosis by suppressing the Nrf2/HO-1 signalling pathway in KRAS mutant colorectal cancer. Cell Death Dis. 2021;10.1038/s41419-021-04367-3.
299. Lin H et al. EF24 induces ferroptosis in osteosarcoma cells through HMOX1. Biomed Pharmacother. 2021;10.1016/j.biopha.2020.111202.
300. Zhou X et al. Flubendazole, FDA-approved anthelmintic, elicits valid antitumor effects by targeting P53 and promoting ferroptosis in castration-resistant prostate cancer. Pharmacol Res. 2021;10.1016/j.phrs.2020.105305.
301. Yao X et al. Simvastatin induced ferroptosis for triple-negative breast cancer therapy. J Nanobiotechnology. 2021;10.1186/s12951-021-01058-1.
302. Zhao L et al. Apatinib induced ferroptosis by lipid peroxidation in gastric cancer. Gastric Cancer. 2021;10.1007/s10120-021-01159-8.
303. Zilka O et al. On the Mechanism of Cytoprotection by Ferrostatin-1 and Liproxstatin-1 and the Role of Lipid Peroxidation in Ferroptotic Cell Death. ACS Cent Sci. 2017;10.1021/acscentsci.7b00028.
304. Chen Y et al. Dihydroartemisinin-induced unfolded protein response feedback attenuates ferroptosis via PERK/ATF4/HSPA5 pathway in glioma cells. J Exp Clin Cancer Res. 2019;10.1186/s13046-019-1413-7.
305. Zheng Z et al. Metformin activates AMPK/SIRT1/NF-kappaB pathway and induces mitochondrial dysfunction to drive caspase3/GSDME-mediated cancer cell pyroptosis. Cell Cycle. 2020;10.1080/15384101.2020.1743911.
306. Zhang CC et al. Chemotherapeutic paclitaxel and cisplatin differentially induce pyroptosis in A549 lung cancer cells via caspase-3/GSDME activation. Apoptosis. 2019;10.1007/s10495-019-01515-1.
307. Zhang X et al. Miltirone induces cell death in hepatocellular carcinoma cell through GSDME-dependent pyroptosis. Acta Pharm Sin B. 2020;10.1016/j.apsb.2020.06.015.
308. An H et al. Tetraarsenic hexoxide enhances generation of mitochondrial ROS to promote pyroptosis by inducing the activation of caspase-3/GSDME in triple-negative breast cancer cells. Cell Death Dis. 2021;10.1038/s41419-021-03454-9.
309. Johnson DC et al. DPP8/DPP9 inhibitor-induced pyroptosis for treatment of acute myeloid leukemia. Nat Med. 2018;10.1038/s41591-018-0082-y.
310. Ren LW et al. Benzimidazoles induce concurrent apoptosis and pyroptosis of human glioblastoma cells via arresting cell cycle. Acta Pharmacol Sin. 2022;10.1038/s41401-021-00752-y.
311. Li Y et al. Dihydroartemisinin induces pyroptosis by promoting the AIM2/caspase-3/DFNA5 axis in breast cancer cells. Chem Biol Interact. 2021;10.1016/j.cbi.2021.109434.
312. Shen Z et al. Metformin inhibits hepatocellular carcinoma development by inducing apoptosis and pyroptosis through regulating FOXO3. Aging (Albany NY). 2021;10.18632/aging.203464.
313. Hu JJ et al. FDA-approved disulfiram inhibits pyroptosis by blocking gasdermin D pore formation. Nat Immunol. 2020;10.1038/s41590-020-0669-6.
314. Yuan R et al. Cucurbitacin B inhibits non-small cell lung cancer in vivo and in vitro by triggering TLR4/NLRP3/GSDMD-dependent pyroptosis. Pharmacol Res. 2021;10.1016/j.phrs.2021.105748.
315. Zang Y et al. Carfilzomib and ONX 0912 inhibit cell survival and tumor growth of head and neck cancer and their activities are enhanced by suppression of Mcl-1 or autophagy. Clin Cancer Res 2012;10.1158/1078 – 0432.CCR-12-1213.
316. Fan TF et al. Dihydromyricetin promotes autophagy and apoptosis through ROS-STAT3 signaling in head and neck squamous cell carcinoma. Oncotarget. 2016;10.18632/oncotarget.10836.
317. Din SRU et al. Latcripin-7A from Lentinula edodes C91-3 induces apoptosis, autophagy, and cell cycle arrest at G1 phase in human gastric cancer cells via inhibiting PI3K/Akt/mTOR signaling. Eur J Pharmacol. 2021;10.1016/j.ejphar.2021.174305.
318. Shen YQ et al. Combination of melatonin and rapamycin for head and neck cancer therapy: Suppression of AKT/mTOR pathway activation, and activation of mitophagy and apoptosis via mitochondrial function regulation. J Pineal Res. 2018;10.1111/jpi.12461.
319. Wang Y et al. Metformin induces autophagy and G0/G1 phase cell cycle arrest in myeloma by targeting the AMPK/mTORC1 and mTORC2 pathways. J Exp Clin Cancer Res. 2018;10.1186/s13046-018-0731-5.
320. Kim KW et al. Autophagy upregulation by inhibitors of caspase-3 and mTOR enhances radiotherapy in a mouse model of lung cancer. Autophagy. 2008;10.4161/auto.6058.
321. Cao C et al. Narciclasine induces autophagy-dependent apoptosis in triple-negative breast cancer cells by regulating the AMPK-ULK1 axis. Cell Prolif. 2018;10.1111/cpr.12518.
322. Harder BG et al. Inhibition of phosphatidylinositol 3-kinase by PX-866 suppresses temozolomide-induced autophagy and promotes apoptosis in glioblastoma cells. Mol Med. 2019;10.1186/s10020-019-0116-z.

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