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Trends in
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Review

The emerging potential role of p62 in cancer treatment by regulating metabolism

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p62 is an important multifunctional adaptor protein participating in autophagy and many other activities. Many studies have revealed that p62 is highly expressed in multiple cancers and decreasing its level can effectively lower the proliferation ability of cancer cells. Moreover, much research has highlighted the significant role of the regulation of cancer cell metabolism in helping to treat tumors. Recent reports demonstrate that p62 could regulate cancer cell metabolism through various mechanisms. However, the relationship between p62 and cancer cell metabolism as well as the related mechanisms has not been fully elucidated. In this review, we describe glucose, glutamine, and fatty acid metabolism in tumor cells and some signaling pathways that can regulate cancer metabolism and are mediated by p62.

Highlights

p62 has been shown to be involved in many signaling pathways related to cancer cell metabolism and plays a crucial role in the regulation of cancer metabolism by participating in the activation or inhibition of these signaling pathways.

p62 could regulate host metabolism through affecting the functions of tumor-infiltrating immune cells.

Therapeutic intervention in cancers through the targeting of p62 is a promising cancer treatment strategy.

Small-molecule compounds targeting the different domains of p62 could potentially be developed for cancer therapy.

Associations between p62 and cancer

p62 [also known as sequestosome-1 (SQSTM1)] is an adaptor protein in the ubiquitination system as well as a cargo protein receptor in selective **autophagy** (see Glossary), so it plays an important role in the regulation of intracellular protein degradation and maintainance of cellular homeostasis. However, recently a large number of bioinformatics analyses and clinical tissue samples show that p62 is highly expressed in a variety of tumor cells and promotes the development of cancer cells [1–3]. For example, researchers found that the overexpression of p62 protein in human hepatocellular carcinoma (HCC) is closely related to the poor prognosis of HCC patients, which indicates that p62 is a potential oncogenic protein [4]. Database analysis has shown that p62 can be considered a prognostic marker of cancer occurrence in melanoma [5]. Furthermore, overexpression of p62 in pancreatic ductal adenocarcinoma (PDAC) helps to maintain protumor inflammation, reduce cancer cell apoptosis, and promote tumor progression [6]. Taking these findings together, p62 plays its oncogenic role by participating in numerous intracellular processes such as cell proliferation, apoptosis, inflammation, oxidative stress response, and autophagy [7–11].

Cancer cells adapt to the harsh tumor microenvironment through metabolic reprogramming to maintain redox states, cell signaling, and biosynthesis. As an emerging hallmark of cancer, cancer metabolism has been reported to be regulated widely for cancer treatment [12,13], and increasing research indicates that p62 modulates cancer metabolism through various mechanisms. Reviews on the regulatory effect of p62 on cancer metabolism are lacking; therefore, this review aims to summarize the most up-to-date information about the relationship between p62 and cancer metabolism as well as some inhibitors targeting p62, which might be further developed into anticancer drugs.

The structure and function of p62

Encoded by *SQSTM1/p62* and located in 5q35, p62 is a multifunctional protein that comprises multiple domains: a Phox and Bem1 (PB1) domain at the N terminus, a ZZ zinc-finger domain,

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a tumor necrosis factor alpha (TNFα) receptor-associated factor 6 (TRAF6) binding (TB) domain, an LC3 interacting region (LIR), a Keap1 interacting region (KIR), and a ubiquitin-associated (UBA) domain at the C terminus [10]. The structure of p62 reflects its potential ability to interact with other partner proteins, which confirms its unique role as a crucial protein in signal transduction. Specifically, as a protein–protein interaction component, the PB1 domain is responsible for facilitating the interaction of p62 with other proteins [14]. The ZZ zinc-finger domain interacts with receptor-interacting protein 1 (RIP1), which is in charge of the activation of nuclear factor kappa B (NF-κB) [15]. The TB domain mediates the association with TRAF6 and LIR is the domain that binds to the autophagosome membrane protein, LC3. In addition, p62 interacts with Keap1 through the KIR domain. Finally, the UBA domain at the C terminus is in charge of the integration of p62 with ubiquitin-tagged proteins and organelles [11], which makes p62 an adaptor protein in the regulation of intracellular protein degradation [3].

Cancer metabolism

It is estimated by the International Agency for Research on Cancer that, in 2020, 19.3 million new cancer cases were identified and about 10 million malignant tumor deaths occurred globally [16]. Due to this serious situation, it is urgent to find effective methods for tumor treatment to improve the therapeutic effect in malignant tumor patients. With increased insight into cancer genetics and biology, the disease has become ever more complex to understand [17]. However, we are delighted that the complexity of the molecular mechanisms has been elucidated by much research on the cancer hallmarks over the years [18–20]. An emerging hallmark of cancer is the reprogramming of energy metabolism. For cancer cells, this involves not only uncontrolled and infinite cell proliferation, but also the corresponding adjustment of energy metabolism to support their rapid growth and division. As many researchers have confirmed the significant role of the regulation of cancer cell metabolism in helping to treat tumors, a better understanding of cancer metabolism will help us further understand how to regulate it. Therefore, based on recently published data, we summarize how glucose, glutamine, and fatty acid metabolism is changed in cancer cells.

Glucose metabolism

Compared with normal cells, cancer cells markedly consume a larger amount of glucose and reprogram their energy metabolism primarily to glycolysis even in the presence of oxygen, which produces energy mainly through the nonoxidative breakdown of glucose, leading to a state called ‘aerobic glycolysis’ that makes tumor cells grow rapidly.

The **Warburg effect** is the essential part of metabolic reprogramming and acts as an important contributor to cancer progression, which leads to at least three consequences: increased glucose consumption, lactate secretion, and reduced respiratory chain activity because of the decreased level of oxidative phosphorylation (OXPHOS) and oxygen consumption [21]. Therefore, cancer cells take advantage of these changes to help them survive in harsh environments. For example, during aerobic glycolysis, many intermediate metabolites are produced for the construction of the cytoskeleton. Moreover, these glycolysis intermediates can also be transferred to certain biosynthetic pathways to generate nucleoside and amino acid intermediates, which in turn promote the biosynthesis of macromolecules that are needed to assemble new cells. For example, NADPH is the direct intermediate of the pentose phosphate pathway (PPP) and can be used to synthetize DNA during cell proliferation. In addition, a greater amount of lactic acid is secreted into the extracellular microenvironment not only to maintain the intracellular acid–base balance but also to induce angiogenesis and facilitate the invasion and metastasis of cancer cells [22]. Oxygen usage is also risky for tumor cells because oxygen and free electrons can interact to produce reactive oxygen species (ROS), which then cause apoptosis [23]. As a result, the

Glossary

ASCT2/Slc1a5: glutamine is imported into the cytoplasm via this transporter.
Autophagy: can be divided into three types – macroautophagy, chaperone-mediated autophagy, and microautophagy [47,48]. In this review, autophagy is referred as macroautophagy which is an intracellular catabolic degradation process that targets excess proteins and some other damaged organelles or cytoplasmic components. Both microautophagy and macroautophagy can be selective or nonselective. Nonselective autophagy is used for the turnover of cytoplasmic constituents under starvation conditions, whereas selective autophagy specifically targets damaged or superfluous organelles [49]. There are many types of selective autophagy in mammalian cells, including mitophagy, aggrephagy, ribophagy, etc. [50]. These terms reflect the recognition and degradation of particular types of cargo. For example, mitophagy means mitochondria are targeted for degradation, aggrephagy refers to the specific degradation of protein aggregates, and ribophagy means that the cargo is ribosomes.
Mammalian target of rapamycin complex 1 (mTORC1): activated or suppressed in response to growth factors, energy, oxygen, DNA damage, amino acids, oncogenes, etc. In addition to these upstream regulators, mTORC1 promotes the synthesis of proteins, lipids, and nucleotides and inhibits autophagy through downstream regulators.
Monocarboxylate transporter 1 (MCT1): a transmembrane protein that transports not only lactate but also H^+.
Nrf2: a transcription factor that controls the expression of over 200 genes involved in the antioxidant stress response. As its binding partner, Keap1 is an adaptor of Cullin3-based ubiquitin ligases. A Keap1 homodimer recognizes a Nrf2 monomer through a two-site binding and hinge latch manner, which is important for the ubiquitination degradation of Nrf2. This mechanism is known as the Keap1-Nrf2 pathway [62].
Warburg effect: normal cells obtain their energy from OXPHOS under aerobic conditions and through glycolysis in the absence of oxygen, but cancer cells strongly depend on glycolysis for energy (ATP) production despite sufficient oxygen supply, which was first observed by Otto Warburg; this

decrease in OXPHOS and oxygen consumption leads to relatively low ROS production in cancer cells that protects against oxidative stress damage, although cancer cells themselves have higher ROS levels than normal cells due to mitochondrial dysfunction and increased metabolism [24].

special glucose metabolism manner is named the Warburg effect [92].

Glutamine metabolism

Glutamine is the most abundant amino acid in plasma because of its wide usage [25]. It acts as a substantial source of reduced nitrogen and carbon by participating in various cellular reactions and serves as a precursor for nucleotide and fatty acid synthesis via reductive carboxylation reactions [20,26]. Therefore, glutamine is of great importance for cancer cell proliferation.

Dependence on an exogenous glutamine supply is a specific metabolic feature of many cancer cells. Exogenous glutamine is commonly imported into the cytoplasm via **ASCT2/Slc1a5**, and due to the critical role of glutamine in cancer cells, various carcinogenic signals can promote the activity of ASCT2. For example, the oncogenic protein c-Myc can upregulate the expression of ASCT2 in neuroblastoma cells through activating transcription factor 4 (ATF4), thus increasing glutamine uptake [27,28]. More importantly, lactate can stabilize c-Myc to increase ASCT2 expression [29]. In addition to the glutamine transporter, cancer cells can obtain glutamine through two other pathways: macropinocytosis and exosomes. Under nutrient-deprived conditions, cancer cells capture extracellular proteins through macropinocytosis and ultimately degrade them in lysosomes and release glutamine into the environment. For example, PDAC cells acquire glutamine in this way [26]. Cancer cells can also obtain glutamine via the uptake of exosomes and release of their cargo, which is necessary to help cell proliferation under nutrient-stress conditions. Therefore, cancer-associated fibroblast-derived exosomes (CDEs) can reprogram cancer cells' metabolism by acting as sources of amino acids under nutrient-deprived conditions in the tumor microenvironment [30].

Fatty acid metabolism

In addition to glucose and glutamine, fatty acid is an important energy source. Cells that grow rapidly require a large amount of fatty acids for new membrane formation and expansion. Therefore, in addition to the external supply, *de novo* synthesis of fatty acids is required for cell membrane synthesis and the rapid proliferation of cancer cells [31]. Recent studies re-emphasize the importance of fatty acid metabolism in cancer progression, because fatty acids are not only structural components but also secondary messengers. Consequently, fatty acid synthesis is of great significance for cell proliferation and cellular responses [25].

Fatty acid synthase (FASN) is a key enzyme during fatty acid synthesis. In normal tissues, the level of FASN is extremely low, while in some cancers, such as breast, stomach, ovarian, and prostate, it is significantly upregulated [32–35]. This is consistent with the fact that cancer cells always increase external lipid uptake to compensate for fatty acid synthesis, and this upregulation especially occurs in metabolically challenging tumor microenvironments such as hypoxia and nutrient deficiency [36]. Moreover, it has been reported that hypoxia inducible factor (HIF)1α promotes fatty acid uptake through increasing the expression of the fatty acid-binding receptors FABP3 and FABP7 and adipose differentiation-related protein (ADRP) in breast cancer cells. KRAS acts as a master regulator of cellular pathways and its activation also promotes extracellular lipid uptake and autophagy [37,38]. In sum, cancer cells use these specific mechanisms to break down metabolic barriers that restrict metabolite synthesis.

The role of p62 in cancer metabolism

As a tumor oncogene, *p62* is frequently abnormally upregulated and tightly involved in the progression of many kinds of tumors, including colorectal, gastric, and pancreatic cancers [39].

Ashley Sample and colleagues utilized a mouse model of skin cancer to show that p62 was necessary for *in vivo* skin tumor growth, and their research supported the carcinogenic role of p62 in tumor development [40]. Another study also showed that p62 could promote cancer progression and metastasis in a breast cancer model by regulating immune cell infiltration [41]. More importantly, overexpression of p62 was enough to induce HCC in the absence of carcinogens or any other additional stimulus [42]. Another previous study also demonstrated that S351-phosphorylated p62 could continuously activate **Nrf2**, thereby reprogramming glucose and glutamine metabolism, which could significantly promote cancer cell survival [43]. Furthermore, Valencia and colleagues found that fibroblasts exhibited decreased glucose uptake when p62 was knocked out [44]. With regard to signaling pathways, p62 is involved in the activation of **mammalian target of rapamycin complex 1 (mTORC1)** in nutrient depletion [45], NF-κB during inflammation and apoptosis [46], and the Keap1-Nrf2 pathway for antioxidant response [47] as well as selective autophagy for the degradation of proteins or damaged organelles. Of note, all of these pathways are closely related to cancer cell metabolism. However, the functions and potential mechanisms of p62 in cancer metabolic reprogramming are complex and remain to be further studied. Here, we summarize the regulatory role of p62 in cancer metabolism.

p62 and glucose metabolism

Regulation of glucose metabolism in cancer cells can be achieved through changes in glucose transporter (GLUT) expression or metabolic enzyme activities. For example, in most situations glucose is transported into the cytoplasm through GLUT proteins and metabolized to pyruvate. In this process, the oncogenes *c-MYC* and *KRAS* can induce overexpression of GLUT1, thus promoting the transport of more glucose into the cells [48–50]. Furthermore, hexokinase-II (HK2) activity is upregulated through increased binding to mitochondria when the phosphatidylinositol 3-kinase (PI3K)/AKT pathway is hyperactivated [51]. In addition to GLUT1 and HK2, isocitrate dehydrogenases (IDHs) are dysregulated in cancer cells [52,53]. In the process of glucose metabolism, it is widely believed that IDH catalyzes the oxidation of isocitrate to generate alpha-ketoglutarate (αKG), which is considered an irreversible enzymatic reaction. However, some identified mutations impaired the ability of IDHs to catalyze the conversion of isocitrate to αKG [52]. It has also been reported that IDH1 mutations can upregulate GLUT1 and induce glucose uptake and lactate production, which involves the PI3K/Akt/mTORC1-HIF1α axis [54].

As reported, p62 can target glucose metabolism directly by interacting with these glucose metabolism enzymes, thereby affecting their levels in cancer cells. For example, some evidence suggests that UBA domain deletion in p62 can increase the localization of HK2 in mitochondria and participate in the process of mitophagy, thereby increasing the level of HK2 [55]. Moreover, clinical HCC samples showed a positive correlation between HK2 and p62 [56]. p62 can increase the mRNA expression level of GLUT1, leading to higher glucose uptake and lactate secretion [44].

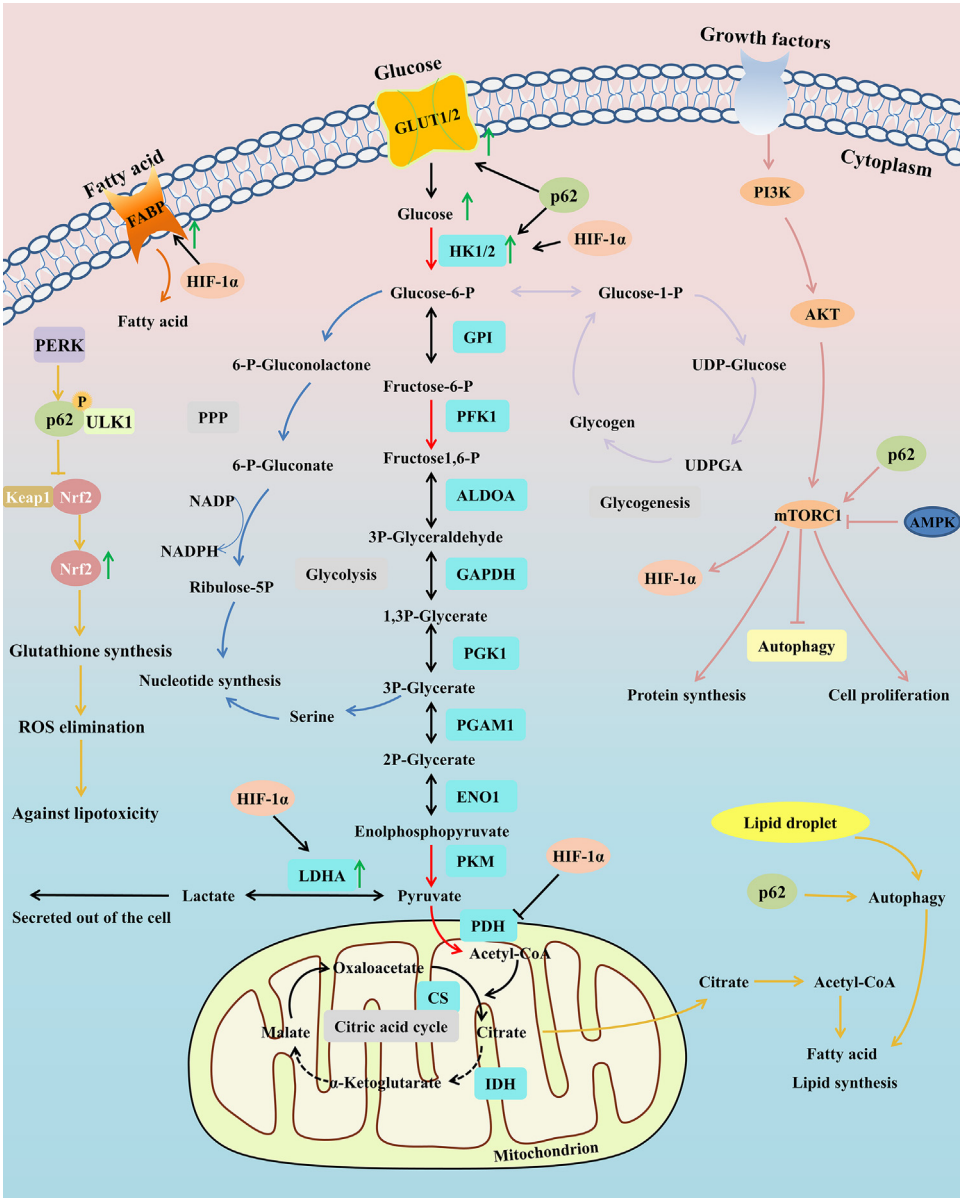
In addition to directly targeting HK2 and GLUT1, p62 can indirectly affect glucose metabolism by regulating other proteins. As an important metabolic reprogramming regulator, HIF1α promotes tumor development and metabolism by upregulating glycolytic pathways and inhibiting mitochondrial respiration [57]. Furthermore, HIF1α and HIF2α levels in tumor tissue biopsies were statistically positively associated with risk of cancer death [58]. Luo and coworkers found that pyruvate kinase M2 (PKM2) could interact with HIF1α in multiple domains through the *in vitro* GST pull-down assay. PKM2 binding to the transactivation domain of HIF1α will stimulate the transcriptional activity of HIF1α, and ultimately PKM2 activates the expression of HIF1α target genes, which encode GLUT and glycolytic enzymes [59]. Due to the vital role of HIF1α in glucose metabolism and the regulatory effect of p62 on HIF1α, p62 plays an increasingly significant role in

the regulation of glucose metabolism. In detail, studies found that p62 knockdown reduced the expression of glycolytic genes such as pyruvate dehydrogenase kinase 1 (PDK1), PKM2, and lactate dehydrogenase A (LDHA) mediated by HIF1α activity [60]. Specifically, the absence of p62 could decrease the transcriptional activity and expression levels of HIF1α by inhibiting mTORC1 activity and NF-κB nuclear translocation. These studies demonstrate that p62 is a critical positive regulator of HIF1α and can regulate glucose metabolism through changing HIF1α activity (Figure 1).

In addition to HIF1α, the NF-κB signaling pathway is important in regulating glucose metabolism. NF-κB comprises five members, which form homodimers or heterodimers. As an inhibitor of NF-κB, IκB protein can bind to NF-κB and inhibit its transcriptional activity, so the activation of NF-κB can be achieved through increasing the degradation of IκB or inhibiting its activity. IκB can be degraded only after it is phosphorylated by the IKK complex and RIP1 can trigger the phosphorylation process mediated by the IKK complex [61]. In F4/80^{hi} macrophages, p62 promoted autophagic degradation of the ubiquitin-editing enzyme A20 that increased RIP1 degradation, leading to enhanced ubiquitination degradation of IκB and activation of NF-κB [62,63]. Another study has shown that inhibition of p62 effectively reduced the activity of NF-κB and the tumor growth rate. Furthermore, after NF-κB was inhibited, the expression of p62 was also decreased, indicating that there was a cyclic relationship between p62 and NF-κB, which led to continuous activation of NF-κB [64]. Finally, it was reported that NF-κB activation led to higher expression of GLUT3, which promoted greater glucose entry into the cytoplasm, thus enhancing glycolysis. In sum, p62 can control metabolic adaptation and energy homeostasis by regulating NF-κB, which plays an important role in glycolysis [65].

In chronic hepatitis B virus (HBV)-infected liver cancers, glucose-6-phosphate dehydrogenase (G6PD) was highly expressed, accompanied by elevated activity of Nrf2 [66]. In hepatocytes, HBV stimulated the expression of G6PD with the help of X protein (HBx) in an Nrf2 activation-dependent pathway. Moreover, Saito and coworkers reported that p62 could interact with Keap1, thus hindering Nrf2 ubiquitination and activating Nrf2 to enhance the hexosamine pathway. In this manner, glutathione synthesis was increased, thus supporting tumor development [43]. These studies suggest that p62 can also maintain energy metabolism through the Keap1-Nrf2 pathway.

Autophagy is also involved in the metabolic reprogramming of tumor cells. As the typical marker protein of autophagy, LC3 mediates the formation of double-membrane vesicles, which capture proteins and damaged organelles to be degraded in the cytoplasm and then combine with the lysosome to form an autophagolysosome. Finally, the decomposed products are released from the autophagolysosome and recycled in the cytoplasm. Therefore, autophagy is of great significance in the life process of all eukaryotic cells, and abnormal autophagy will result in various metabolic diseases, such as cancers [67] and infectious diseases [68]. Although autophagy has a dual effect on cancer progression, which has been widely studied (Box 1), autophagy is a crucial contributor to the maintenance of cellular homeostasis. Autophagy regulates cancer metabolism mainly through three mechanisms: providing essential components for energy demand; ensuring energy supply by controlling mitochondrial quality and dynamics; and regulating the levels of some enzymes in metabolic pathways [69]. An analysis of key metabolites confirmed that autophagy-defective newborn rats have a systemic amino acid deficiency and decreased glucose levels. This proved that autophagy plays an important role in glucose metabolism [70]. In addition, previous studies have found that cholangiocarcinoma cells with cisplatin resistance have higher levels of glucose uptake, consumption, lactic acid production, and PPP activity. By examining p62 and LC3 expression, researchers found that cholangiocarcinoma cells had a higher



Trends in Endocrinology & Metabolism

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Box 1. Autophagy has a dual effect on cancer progression

Differences in cancer type, stage, and genetic background determine whether autophagy promotes tumor cell proliferation or death [93]. When the function of autophagy is affected, it will lead to the accumulation of abnormal proteins and organelles and cause a variety of diseases such as tumors and neurodegenerative diseases. When cells are deficient in nutrients, they can break down macromolecules (e.g., nucleic acids, proteins, lipid droplets) by autophagy to produce nucleotides, glucose, amino acids, and fatty acids. In this manner, autophagy-mediated macromolecular degradation results in the recycling of basic components that support the main metabolic needs of cancer cells [94]. In this sense, autophagy has been suggested to protect tumor cells against metabolic stress-induced death, and elevated autophagy will lead to the degradation of metabolic waste, which is required by tumor cells to maintain cellular homeostasis and help them survive under nutrient stress.

autophagic flux. After being treated with chloroquine (CQ), an autophagy inhibitor, cholangiocarcinoma cells became more sensitive to cisplatin. CQ might inhibit the interaction between glucose metabolism signaling and autophagy by blocking the autophagy-lysosome pathway, increasing the production of intracellular hydroxyl radicals, which ultimately resulted in the reduced cellular antioxidant capacity [71]. In this sense, more ROS would be produced in the intracellular mitochondria to strengthen cisplatin sensitivity.

p62 and glutamine metabolism

As the most commonly deficient amino acid, glutamine has two major uses after being imported into tumor cells. One is that glutamine provides the cells with essential nitrogen and carbon sources, the other is that glutamine participates in the synthesis of glutathione, an important antioxidant [25]. Some studies have indicated that p62 could regulate some factors tightly associated with glutamine uptake and biosynthesis [44]. For example, p62 upregulated Slc1a5 expression and thus increased glutamine uptake. In addition, the expression of glutamate cysteine ligase (GCL), NAD(P)H:quinine oxidoreductase 1 (NQO1), and sulfiredoxin-1 (Srxn1), which affect glutathione synthesis and utilization, was decreased on lowering of the p62 level [72]. It was also noteworthy that Lam and coworkers found that p62-knockdown $Tsc2^{-/-}$ MEFs exhibited 50% reduced glutamine uptake compared with the control group. Through metabolite set enrichment analysis, they found that the loss of p62 downregulated certain pathways, including glutathione metabolism and nucleotide biosynthesis, all of which depended on glutamine as an essential precursor for biosynthesis.

mTORC1 acts as a key nutrient sensor by controlling the balance between anabolism and catabolism [73] (Figure 2). Normal cells always increase their production of nucleotides and fatty acids but suppress catabolic processes such as autophagy to multiply and respond to complex environmental input changes through the activation of mTORC1. Research has shown that, under

Figure 1. The role of p62 in regulating cancer glucose and fatty acid metabolism. Glucose and fatty acid metabolism can be regulated by p62 and various oncogenes such as *phosphatidylinositol 3-kinase* (*PI3K*)/*AKT*, *Nrf2*, and *hypoxia inducible factor* (*HIF*)*1*. p62 is a potent activator of the Warburg effect, promoting lactic acid production and glucose uptake. First, as one of the key glycolytic enzymes, hexokinase-II (HK2) binds to the outer mitochondrial membrane protein voltage-dependent anion-selective channel 1 (VDAC1) and thereby directs ATP production in the mitochondria, preferentially providing a constant energy supply for HK2 catalyzing glycolysis. The ubiquitin-associated (UBA) domain of p62 increases the mitochondrial localization of HK2. In addition, p62 can increase the mRNA expression level of glucose transporter 1 (GLUT1), leading to greater glucose uptake. p62 also triggers a dramatic enhancement of HIF1α stability, which leads to increased levels of fatty acid-binding receptor proteins (FABPs) and lactate dehydrogenase (LDHA). Last, p62 promotes glutathione synthesis by activating the Keap1-Nrf2 pathway to counteract lipotoxicity and promotes the decomposition of lipid droplets through autophagy to increase the synthesis of fatty acids. Abbreviations: ALDOA, aldolase A; CS, citrate synthetase; ENO1, enolase 1; GPI, glucose phosphate isomerase; IDH, isocitrate dehydrogenase; mTORC1, mammalian target of rapamycin complex 1; PDH, pyruvate dehydrogenase; PERK, protein kinase R-like endoplasmic reticulum kinase; PFK1, phosphofructokinase-1; PGAM1, phosphoglycerate mutase 1; PGK1, phosphoglycerate kinase; PKM, pyruvate kinase M; PPP, pentose phosphate pathway; ROS, reactive oxygen species; UDPGA, UDP-glucuronic acid; ULK1, unc-51-like kinase 1.

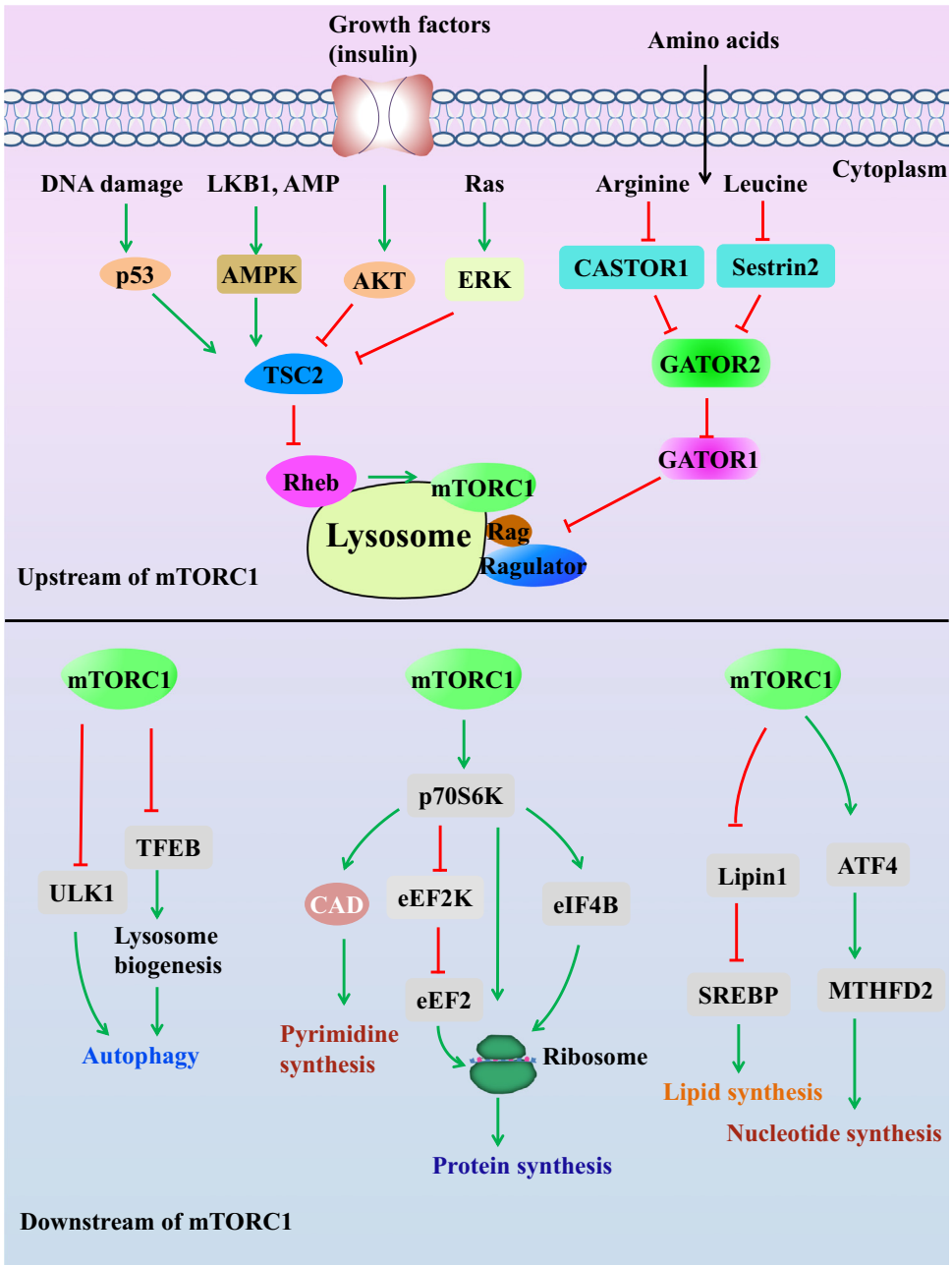


Figure 2. The major upstream regulators and downstream pathways of mammalian target of rapamycin complex 1 (mTORC1). mTORC1 is activated or suppressed in response to amino acids, growth factors, and DNA damage. The activation of mTORC1 leads to an increase in protein, lipid, and nucleotide synthesis as well as autophagy inhibition. The green lines in the figure show promoting effects and the red lines indicate inhibiting effects. Abbreviations: p70S6K, p70 ribosomal protein S6 kinase; ATF4, activating transcription factor 4; CAD, carbamoyl-phosphate synthetase; CASTOR1, cellular arginine sensor for mTORC1; eEF2K, eukaryotic elongation factor 2 kinase; eIF4B, eukaryotic initiation factor 4B; SREBP, sterol responsive element binding protein; TFEB, transcription factor EB; TSC2, tuberous sclerosis complex 2; ULK1, unc-51-like kinase 1.

conditions with sufficient amino acids, p62 was first phosphorylated through strengthening of the interaction between its PB1 domain and mitogen-activated protein kinase kinase 3 (MEKK3) [74]. Next, p62 interacted with mTORC1 and Rag, which recruited the ubiquitin ligase TRAF6 and mTORC1 to the lysosome surface, finally leading to the ubiquitination and activation of mTORC1 [62]. Taken together, these studies revealed the prominent role of p62 in maintaining metabolic homeostasis through regulation of the ubiquitination modification of mTORC1 (Figure 3). Recent research found that knockdown of p62 could not only inhibit cell proliferation, but also inhibit the AKT/AMPK/mTOR pathway to decrease the proliferation of papillary thyroid carcinoma (PTC) [3]. In a word, these findings demonstrated the decisive role of p62 in helping

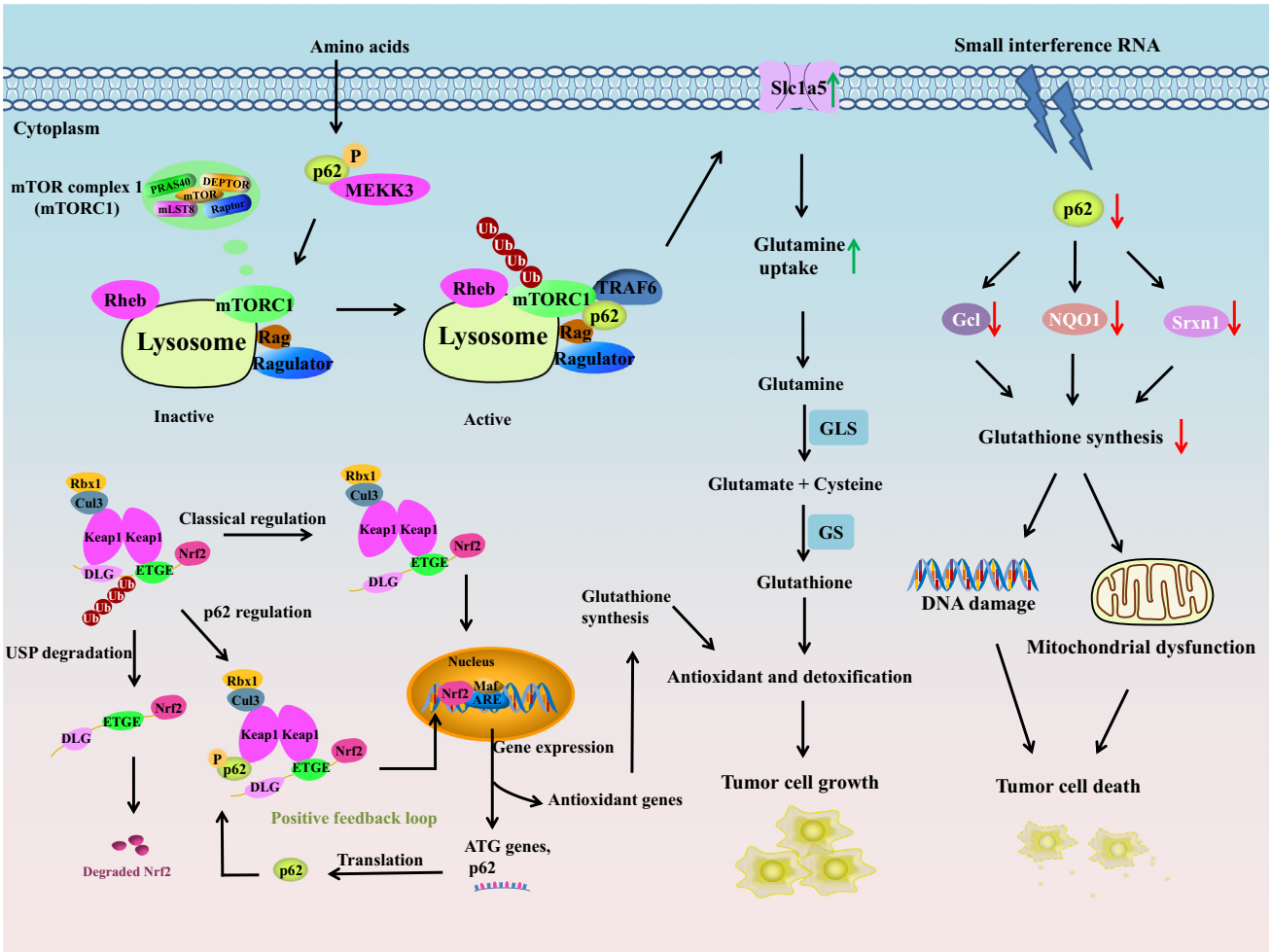


Figure 3. The role of p62 in regulating glutamine metabolism. p62 stimulates glutamine uptake and glutathione synthesis by activating the mammalian target of rapamycin complex 1 (mTORC1) and Keap1-Nrf2 pathways. In mTORC1, mTOR binds to Raptor, which is responsible for mTORC1 subcellular localization and substrate recruitment. Amino acid stimulation promotes the phosphorylation of p62 by mitogen-activated protein kinase kinase 3 (MEKK3), which forms signaling hubs on the lysosome membrane through the interaction between the p62, Raptor, tumor necrosis factor alpha receptor-associated factor 6 (TRAF6), and Rag proteins. As a result, mTOR is ubiquitinated by TRAF6 and then activated, which leads to increased levels of the glutamine transporter Slc1a5 that promotes tumor cell growth. At the same time, Keap1 participates in glutathione synthesis. Under normal conditions, Keap1 collaborates with the Cul3/Rbx1 E3 ubiquitin ligase complex, promoting the proteasomal degradation of Nrf2. However, on oxidative stress, Keap1 oxidation results in the liberation of Nrf2 thus facilitating its translocation to the nucleus. Furthermore, phosphorylated p62 interacts with Keap1 and competitively inhibits the Keap1-Nrf2 interaction, which leads to the expression of antioxidant genes and helps tumor cells grow. However, when p62 is knocked down, the expression of Gcl, NQO1, and Srxn1 related to glutathione synthesis and utilization is also decreased. This results in DNA damage and mitochondrial dysfunction, leading to tumor cell death. Abbreviations: GLS, glutaminase; GS, glutamine synthetase.

to maintain intracellular glutathione pools through the modulation of glutamine metabolism, glutathione biosynthesis, and redox homeostasis in mTORC1-driven tumor cells [72].

Usually, Nrf2 activation can be achieved through some proteins competitively binding with Keap1 to interfere with the degradation of Nrf2. As mentioned earlier, p62 has a KIR that binds to Keap1, resulting in Keap1being no longer able to interact with Nrf2 [75]. On persistent activation of Nrf2, cancer cells will benefit from metabolic reprogramming because Nrf2 regulates the expression of genes involved in glutathione synthesis, glutaminolysis, and autophagy [43,76] (Figure 3). Studies by Saito have shown that phosphorylation of p62 at Ser349 directed glutamine towards the glutathione synthesis pathway through the activation of Nrf2, which makes HCC cells resistant to anticarcinogens and gives the potential for rapid proliferation. Moreover, increased levels of p62 provided cancer cells with an improved antioxidant response due to Nrf2 activation, together with a proangiogenic and prosurvival effect because of NF-κB activation, both of which promoted the occurrence and progression of tumors [62]. Taken together, these results indicated that p62 could change the oxidative stress state and affect glutamine metabolism in an Nrf2-dependent manner.

p62 and fatty acid metabolism

Similar to glucose and glutamine, fatty acid synthesis is vital for cancer cell proliferation. The synthesis of fatty acid requires abundant NADPH, which not only contributes to the anabolism that supports cell growth but also acts as a biological reducing agent to protect cells against death caused by oxidative stress [25]. A previous study stated that excessive saturated fatty acid could produce extensive ROS, and ROS-mediated cell death was still the critical reason for hepatic lipotoxicity; however, the Keap1-Nrf2 pathway was responsible for ROS elimination, which could be activated by the p62-Unc-51-like autophagy activating kinase 1 (ULK1) axis [77]. Recent results indicated that HIF1α could increase fatty acid uptake and lipid storage, which contributed to cell survival [36]. Furthermore, lipid droplets could be degraded into fatty acids by p62-mediated autophagy to support the energy demand of cancer cells (Figure 1). More interestingly, Huang and colleagues showed that p62 deficiency repressed adipocytes' energy consumption but increased nutrient availability for prostate tumors [78]. Therefore, the role of p62 in fatty acid metabolism is complex and more mechanisms need to be elucidated.

The microenvironmental regulation of cancer metabolism induced by p62

Increasing epidemiological evidence highlights the tremendous impact of cancer progression on host metabolism, especially in cachexia. For example, lactate was secreted into the extracellular environment of tumor cells through **monocarboxylate transporter 1 (MCT1)** and resulted in acidification of the tumor microenvironment, which made it easier for tumor cells to invade the adjacent adipose tissue, resulting in adipocyte lipolysis. The tumors also caused distant adipose tissues to shut down some main metabolic processes that were antagonized by p62, ultimately leading to reduced lipid storage in adipocytes [20,79]. In this way, cancer cells could obtain more lipids, which ensured the maintenance of their rapid proliferation and survival in changed environments. Interestingly, previous data also revealed that p62 served as a latent metabolic tumor suppressor while orchestrating the symbiotic collaboration between adipose tissue and tumors by regulating cancer metabolic fitness [79]. With regard to stromal fibroblasts, tumor epithelium impaired metabolic detoxification and the release of ROS via the inhibition of p62, c-Myc, and mTORC1 activity in stromal fibroblasts [44]. In addition to the regulatory effect of tumors on host metabolism, tumor cells also have an effect on immune cells in the tumor microenvironment. Macrophages are divided into M1 and M2 types, which differ in their immune function and metabolism [80]. Activation of the M1 type usually leads to highly inflammatory macrophages with high phagocytic and bactericidal potential. M2 macrophages participate in tissue repair and wound

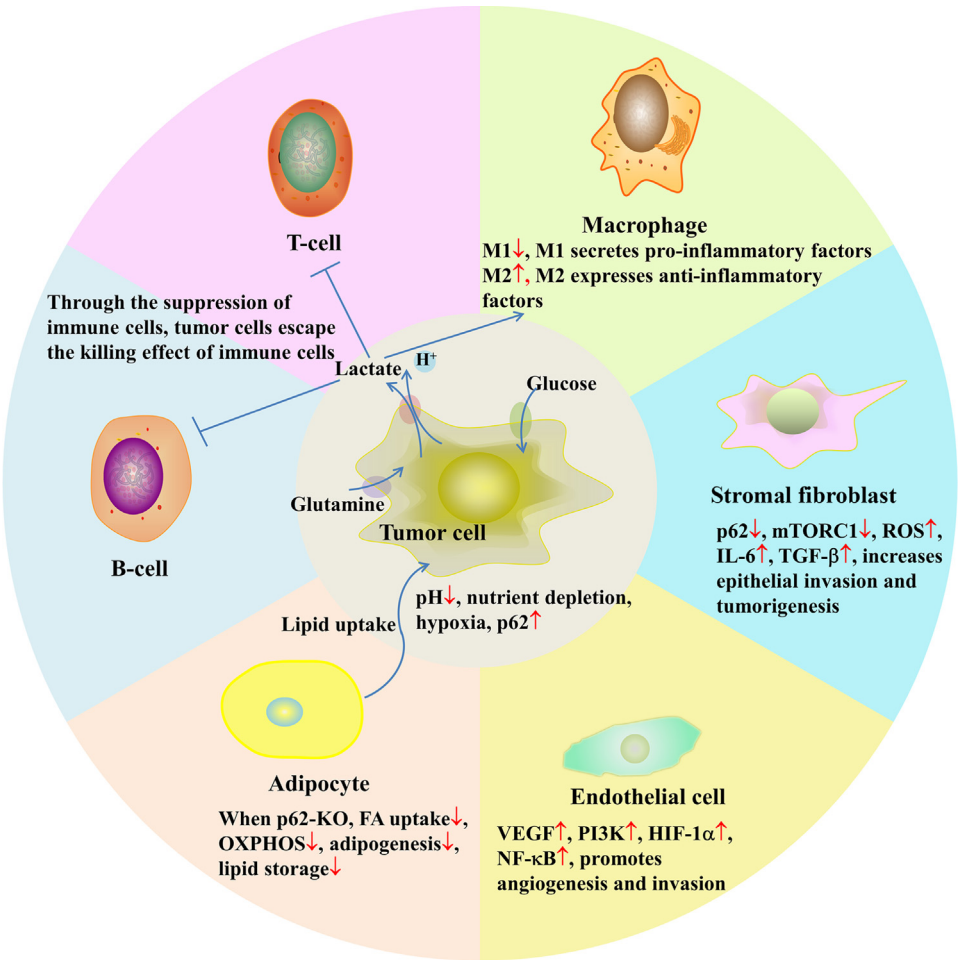


Figure 4. Metabolic crosslink between tumor cells and other cells in the tumor microenvironment. The complex tumor microenvironment increases tumor cell survival and proliferation, stimulates angiogenesis, and results in suppression of the immune response through the alteration of several types of infiltrating immune cells. Abbreviations: FA, fatty acid; HIF-1α, hypoxia inducible factor 1α; IL-6, interleukin-6; KO, knockout; mTORC1, mammalian target of rapamycin complex 1; NF-κB, nuclear factor kappa B; OXPHOS, oxidative phosphorylation; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor.

healing [81]. Usually, tumor-associated macrophages (TAMs) have a special transition period from the M1-like to M2-like phenotype. At the early stage of tumor initiation, TAMs are the M1-like phenotype before transforming to the M2-like type [82]. p62 can increase the secretion of lactate in tumor cells by regulating glucose metabolism, leading to acidification of the tumor microenvironment. Strikingly, the lactate secreted into the tumor microenvironment could lead macrophages to M2-like phenotype polarization [83], and contribute to tumor evasion. Not only nutrient restriction but also tumor-induced changes in metabolite abundance or the accumulation of metabolic waste products (e.g., lactate) could trigger local immunosuppression, thus facilitating tumor progression and metastasis [84]. Thus, lactate production and the pH changes induced by lactate secretion can affect both tumor cells and immune cells [85]. For example, Haas and colleagues demonstrated that lactate inhibited the proliferation and activation of T cells *in vitro* [86]. In addition, Hayes and coworkers summarized the inhibitory effect of lactic

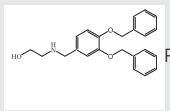
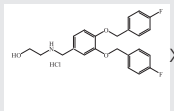
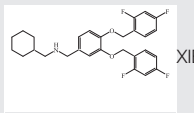
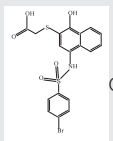
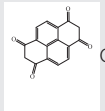
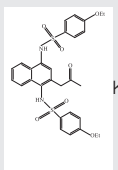
acid on B cells [87]. The aforementioned complex metabolic associations triggered by p62 between cancer cells and other cells are shown in Figure 4.

Small-molecule modulators targeting p62

Due to the regulatory effect of p62 on cancer cell metabolism, p62 is becoming a promising therapeutic target. Therefore, the design and development of small-molecule inhibitors targeting p62 is of great significance. Although drugs targeting p62 are not yet on the market, some reported molecules affecting p62 levels through targeting other proteins might be noteworthy [10,88], as shown in Table 1.

The ZZ domain of p62 participates in NF-κB signaling pathways, and the development of inhibitors that target the ZZ region may be a promising strategy. Compound P62XIE3 was one of the initial molecules targeting the ZZ domain of p62. Xie's group demonstrated that its IC_{50} in multiple myeloma (MM) was 6.19 μM [95]. Moreover, Xie's group also found another p62-ZZ inhibitor, XRK3F2, with an IC_{50} of 4.35 μM in the MM1.S cell line [89,96]. Another p62-ZZ inhibitor was XIELP1-17b, which had an IC_{50} of 0.84 μM also in the MM1.S cell line [97]. The LIR region of p62 is responsible for autophagic degradation, and specific inhibitors of this interaction are also required. Based on the two-colored fluorescence correlation spectroscopy (FCS) competitive binding assay, Tsuganezawa and coworkers found two selected LC3–p62 interaction inhibitors

Table 1. Representative small-molecule modulators targeting p62

Compound	Target	Indication	IC_{50}	Refs
 P62XIE3	ZZ domain of p62	MM	6.19 μM	[95]
 XRK3F2			4.35 μM	[89,96]
 XIELP1-17b			0.84 μM	[97]
 Compound 1	LC3–p62 interaction	–	0.9 μM	[90]
 Compound 2		–	2.0 μM	[90]
 K67	Keap1–p62 interaction	HCC	1.5 μM	[43]
	Keap1–Nrf2 interaction		6.2 μM	[43]

with IC_{50} values less than 2 μM: Compound 1 and Compound 2 [90]. In addition, a previous study identified K67, a small-molecular compound that inhibited the interaction between p-p62 and Keap1 with an IC_{50} value of 1.5 μM in the fluorescence polarization (FP) assay [43]. K67 removed the phosphorylated p62 from Keap1 and restored the activity of Keap1 in liver cancer cells, thus leading to the ubiquitination degradation of Nrf2. Their research also showed that HCC cells treated with K67 exhibited suppressed proliferation and enhanced susceptibility to cisplatin. In sum, inhibitors targeting Keap1-p62 could prevent Nrf2 activation, therefore contributing to the treatment of HCC. However, K67 had a low selectivity because it inhibited not only the Keap1–p62 interaction but also the Keap1–Nrf2 interaction with an IC_{50} of 6.2 μM [91]. Therefore, a highly selective compound is still indispensable.

Concluding remarks

Being at the crossroads of many cellular pathways, p62 plays a crucial role in the regulation of cancer metabolism. As stated in our review, p62 can regulate glucose, glutamine, and fatty acid metabolism through many signaling pathways, such as NF-κB, Nrf2, and mTORC1. Recent studies have shown that the development of small-molecule inhibitors targeting p62 is also a potential chemotherapeutic approach against HCC. Although p62 may be a promising target for cancer treatment, very few molecules targeting p62 have been synthesized at present because whether p62 is a potential target needs further confirmation and the mechanisms of how p62 regulates cancer cell metabolism need to be explored in depth (see Outstanding questions). Therefore, the therapeutic effect of p62 on cancer cells deserves further discussion and consideration. To better elucidate how p62 regulates cancer metabolism, a combined approach of metabolomics and clinical sample analysis may be necessary. Further studies in animal models and humans are also needed to fully clarify the metabolic alterations caused by p62. However, on account of the important role of p62 in cancer metabolism and because targeting cancer cell metabolism is a potential strategy to treat cancers, it remains urgent to design and exploit more effective small-molecule drugs for p62. In addition, p62 is widely distributed and has different or even opposite effects in different tumor cells. How to improve the targeting activity and tissue selectivity of p62 inhibitors is another problem that we should consider carefully in future research (see Outstanding questions).

Outstanding questions

How the p62 expression levels of neighboring cells in the tumor microenvironment affect cancer cells has not been fully elucidated.

Whether p62 is a potential target for cancer therapy needs more confirmation and how p62 regulates tumor metabolism in different cancer cells needs to be explored in more depth and exhaustively.

Few p62 inhibitors have been developed, so more small-molecule inhibitors targeting p62 are still needed.

Because p62 has different or even opposite effects on tumor cells, immune cells, adipocytes, and stromal fibroblasts, the roles of p62 in cancer metabolism in different contexts should be clarified. These findings may require small-molecule inhibitors have good tissue selectivity.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that have appeared to influence the work reported in this review.

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