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Glutaminolysis and autophagy in cancer

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Abbreviations: αKG, α-ketoglutarate; AKT1/PKB, v-akt murine thymoma viral oncogene homolog 1; AMPK, 5′-AMP-activated protein kinase; ATG, autophagy related; ATM, ATM serine/threonine kinase; BCL2, B-cell CLL/lymphoma 2; BECN1, Beclin 1, autophagy related; BNIP3, BCL2/adenovirus E1B 19kDa interacting protein 3; BPTES, bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulphide; DDR, DNA damage response; DON, 6-diazo-5-oxo-L-norleucine; EGCG, epigallocatechin gallate; FAN1/FANCD2, FANCD2/FANCI-associated nuclease 1; FOXO3, forkhead box O3; GLS/GLS1/KGA, glutaminase; GLS2/LGA, glutaminase 2 (liver mitochondrial); GLUD1, glutamate dehydrogenase 1; GLUL, glutamate-ammonia ligase; GSH, glutathione; MAPK8/JNK1, mitogen-activated protein kinase 8; MAP1LC3, microtubule-associated protein 1 light chain 3; MTOR, mechanistic target of rapamycin; MTORC1, mechanistic target of rapamycin complex 1; MTORC2, mechanistic target of rapamycin complex 2; NADPH, nicotinamide adenine dinucleotide phosphate; SQSTM1/p62, sequestosome 1; EGLN/PHD, egl-9 family hypoxia-inducible factor; RB1CC1/FIP200, RB1-inducible coiled-coil 1; RRAG, Ras-related GTP binding; RHEB, RAS homolog enriched in brain; ROS, reactive oxygen species; SLC1A5, solute carrier family 1 (neutral amino acid transporter) member 5; SLC7A5, solute carrier family 7 (amino acid transporter light chain, L system), member 5; SLC3A2, solute carrier family 3 (amino acid transporter heavy chain), member 2; TCA, tricarboxyic acid; TFEB, transcription factor EB; TSC, tuberous sclerosis; ULK1/2, unc-51 like autophagy activating kinase 1/2.

The remarkable metabolic differences between cancer cells and normal cells result in the potential for targeted cancer therapy. The upregulation of glutaminolysis provides energetic advantages to cancer cells. The recently described link between glutaminolysis and autophagy, mediated by MTORC1, may constitute an attractive target for therapeutic strategies. A combination of therapies targeting simultaneously cell signaling, cancer metabolism, and autophagy can solve therapy resistance and tumor relapse problems, commonly observed in patients treated with most of the current targeted therapies. In this review we summarize the mechanistic link between glutaminolysis and autophagy, and discuss the impacts of these processes on cancer progression and the potential for therapeutic intervention.

Introduction

Mammalian cells control their proliferation very tightly to maintain intracellular homeostasis and tissue architecture and function. In contrast, cancer cells exhibit several features that impair this homeostasis, such as uncontrolled proliferation and metabolic reprogramming, among others.[1] The high proliferation exhibited by cancer cells requires both the deregulation of proliferative control and a constant supply of nutrients. Thus, tumor cells acquire mutations in genes regulating proliferation, allowing cell growth independently of proliferative cues.[2] To satisfy their high demand for nutrients, cancer cells undergo a metabolic reprogramming that stimulates anabolism through numerous metabolic pathways. Those pathways ultimately lead to a high dependency of the cancer cell on specific nutrients.[3] Among those nutrients, glutamine has been described as crucial for many types of tumors.[4-8] This amino acid is metabolized within the mitochondrion through an enzymatic process termed glutaminolysis, whereby glutamine is converted to α-ketoglutarate (αKG), an intermediate of the tricarboxylic acid (TCA) cycle.[9] In highly proliferating cells, citrate produced in the TCA cycle is redirected into the cytosol for the production of NADPH and fatty acids. The production of αKG though glutaminolysis replenishes the TCA cycle, a process called anaplerosis.[10,11] However, as we will discuss in this review, anaplerosis is not the only advantage provided by glutaminolysis to proliferating cancer cells.[4,10,12]

The high proliferation rate of cancer cells, along with the excessive anabolism occurring within the tumor, leads to a limited nutrient accessibility, to a hypoxic context, and to a leak of electrons within the mitochondria of tumor cells.[13] Those conditions partially account for the increased levels of reactive oxygen species (ROS) exhibited by cancer cells, which, in turn, induce additional mutations in the DNA, as well as damage in macromolecules and organelles.[13] Glutamine and leucine are potent inhibitors of macroautophagy (hereafter referred as autophagy), a key catabolic mechanism that cells use to degrade long-lived proteins and organelles.[14] The major downstream effector mediating this inhibition is the mechanistic target of rapamycin complex 1 (MTORC1), a central regulator of cell growth, mRNA translation, autophagy, and metabolism.[15-17] The mechanism underlying the detection of amino acids by MTORC1 is not completely

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understood.[18,19] The remarkable rearrangement of the cellular metabolism during malignant transformation frequently correlates with the hyperactivation of MTORC1.[20] However, autophagy is not necessarily low in all tumors that display hyperactive MTORC1, and the significance of these events for cancer remains to be fully understood. The mechanistic connection between glutaminolysis and MTORC1, and their effect on autophagy, constitute an attractive source of targets for the development of future therapies against cancer. In this review, we discuss the connection between glutaminolysis and autophagy in cancer progression, and their impact on molecular therapies targeting metabolic transformation.

Glutamine metabolism and malignant transformation

Glutamine is the most abundant free amino acid in the blood and a main physiological source of nitrogen in mammalian cells.[4,5] Nevertheless, despite being a nonessential amino acid from a biochemical point of view, glutamine becomes physiologically essential in conditions of high proliferation.[21] The increased consumption of glutamine has been linked to the dysregulation of oncogenes and tumor suppressors.[22,23] Thus, Wise et al.[22] in 2008 described the finding that MYC increases the expression of the cellular transporter of glutamine, and enhances the consumption of glutamine in cancer cells. Through glutaminolysis, glutamine is first deamidated to glutamate, in an irreversible reaction catalyzed by the enzyme GLS (glutaminase). Then, glutamate is further deaminated to αKG by the enzyme GLUD1/GLUD (glutamate dehydrogenase) (**Fig. 1**).[9] GLS exists in 2 isoforms, GLS/GLS1/KGA (the kidney-type) and GLS2/LGA (the liver-type), encoded by the genes *GLS* and *GLS2*, respectively.[24] GLS, which is the isoform that mainly accounts for the glutaminase activity of tumor cells, is inhibited by glutamate and is distributed ubiquitously.[25,26] In contrast, GLS2 is mainly expressed in the liver and cannot be inhibited by glutamate.[24,25,27] Additionally, whereas GLS2 is activated by ammonium, GLS is not.[28,29] As glutamate levels regulate the activity of GLS, the production of αKG through glutaminolysis also requires an increase in the activity of GLUD1. Importantly, leucine, a key amino acid from a signaling standpoint, is an allosteric activator of GLUD1, and thus, upregulates the production of αKG from glutamate, preventing the inhibition of GLS.[30,31] This cooperative effect between glutamine and leucine is also observed at the level of membrane transporters. Glutamine is taken up by the cell through the transporter SLC1A5. Thereafter, glutamine is extruded from the cell by a dimeric bidirectional antiporter termed SLC7A5-SLC3A2, which at the same time introduces leucine inside the cell.[32] Thus, glutamine modulates the intracellular levels of leucine, which in turn activates GLUD1, enhancing the production of αKG via glutaminolysis. Mitochondrial αKG can be exported to the cytosol through SLC25A11, the mitochondrial αKG/malate carrier protein, in exchange for cytosolic malate (**Fig. 1**). Net release of αKG from the mitochondria toward the cytosol occurs when malate recycles in exchange for cytosolic phosphate.[33,34]

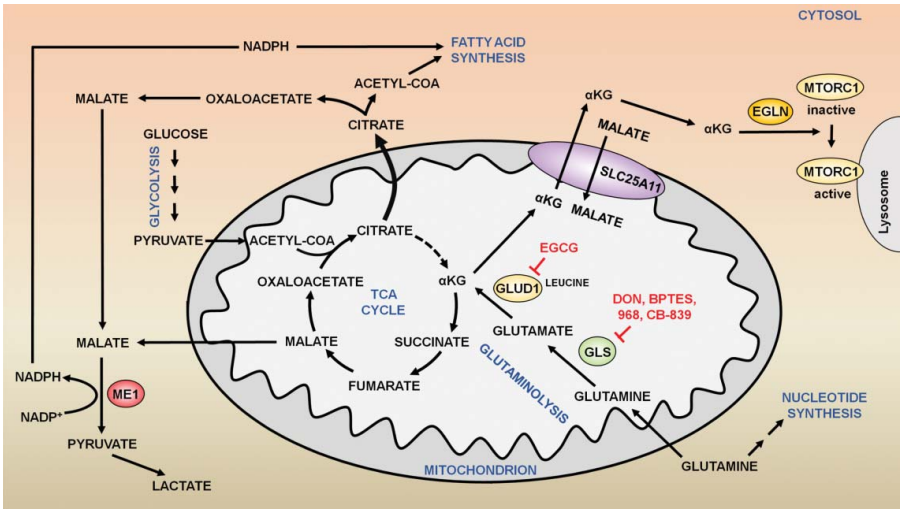

Figure 1. Glutamine metabolism and metabolic transformation. In highly proliferating cells, citrate is diverted away from the TCA cycle for the synthesis of lipids. In the cytoplasm, citrate is converted to acetyl-CoA and oxaloacetate by the enzyme ACLY (ATP citrate lyase). While acetyl-CoA is used for the synthesis of lipids, oxaloacetate is converted to malate. Cytosolic malate is converted to pyruvate and NADPH by ME (malic enzyme). GLS (glutaminase) deamidates glutamine into glutamate. Thereafter, glutamate is further deaminated by the enzyme GLUD1 (glutamate dehydrogenase 1) to yield αKG, which replenishes the TCA cycle. In addition, glutaminolytic αKG can be exported into the cytosol through SLC25A11, the mitochondrial αKG/malate carrier protein, where this metabolite activates EGLNs, which in turn activate MTORC1 to promote cell growth and anabolism. Several inhibitors of glutaminolysis (DON, BPTES) have shown a capacity to reduce MTORC1 activation and cell growth in cancer cells.

Proliferating cancer cells require high quantities of fatty acids and lipids to generate new membranes. To sustain the synthesis of fatty acids, citrate is diverted away from the TCA cycle to synthesize acetyl-CoA and oxaloacetate in the cytosol,[35] a process catalyzed by the enzyme ACLY/ATP citrate lyase. Oxaloacetate resulting from this reaction as a co-product is then converted to malate, which subsequently is catalyzed by ME1 (malic enzyme 1, NADP[+]-dependent, cytosolic) for the production of NADPH, necessary for the synthesis of fatty acids (**Fig. 1**).[34,36] As a consequence, the TCA cycle is disrupted, compelling cancer cells to consume alternative nutrients to re-establish the TCA cycle. Thus, as glutamine along with leucine stimulates the production of αKG, the increase in glutaminolysis is a metabolic advantage for tumor cells, reconstituting the TCA cycle (**Fig. 1**). Nonetheless, cancer cells consume more glutamine than the quantity required to just replenish the TCA cycle.[36] Therefore, besides anaplerosis, the excessive consumption of glutamine must provide other advantages to the cancer cell. Indeed, a fraction of the malate

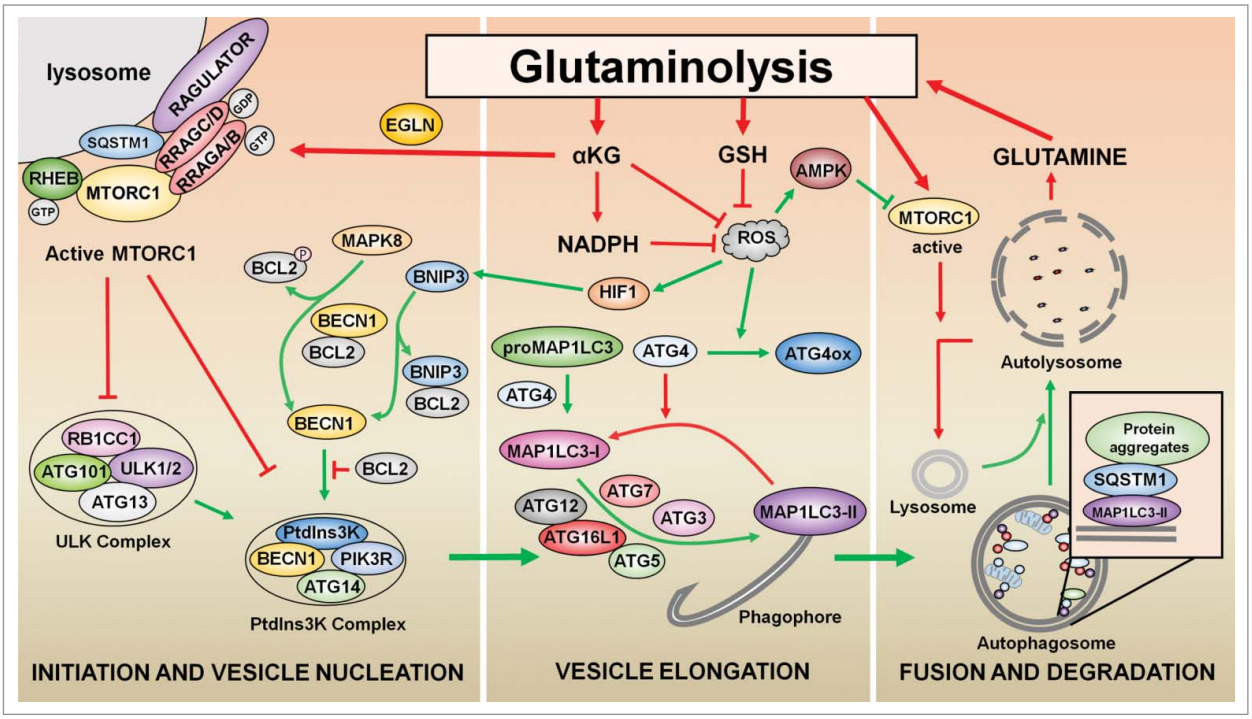

Figure 2. Regulation of autophagy by glutaminolysis. The generation of αKG by glutaminolysis activates EGLNs, which in turn promote MTORC1 activation. MTORC1 inhibits both the phosphatidylinositol 3-kinase (PtdIns3K) complex and ULK complex to prevent the initiation and vesicle nucleation steps of autophagy. The production of GSH, NADPH, and αKG by glutaminolysis limits the production of ROS to counteract the induction of autophagy. The accumulation of ROS induces the oxidation of ATG4, thus preventing the delipidation of the autophagy marker MAP1LC3-II, and activates MAPK8, which results in the dissociation of the BECN1-BCL2 complex. Under hypoxia, HIF1 induction activates BNIP3, which binds to BCL2 to activate autophagy by disrupting the interaction between BECN1 and BCL2. Finally, the reactivation of MTORC1 by glutaminolysis is necessary for lysosome regeneration and autophagy termination. Green arrows indicate processes that result in autophagy activation; red arrows indicate processes that result in autophagy inhibition.

produced from glutaminolytic αKG in the TCA cycle translocates into the cytosol, where it is converted to pyruvate by ME1.[36] In addition, glutamate produced by GLS is necessary for the synthesis of glutathione (GSH), an intracellular antioxidant that contributes to mitigate the oxidative stress in proliferating cells (**Figs. 2, 3**).[37] Glutamine is also a crucial donor of nitrogen for the synthesis of purines and pyrimidines.[38] Finally, as described above, the cooperative effect of glutamine and leucine in the production of αKG converges in the activation of signaling pathways that promote cell growth. Glutaminolytic αKG enhances the GTP loading of RRAG proteins, and thus activates MTORC1 and inhibits autophagy (**Figs. 2, 3**).[39,40] Conversely, the withdrawal of growth factors leads to the activation of FOXO3, which in turn, increases the expression of GLUL (glutamate-ammonia ligase), the enzyme that resynthesizes glutamine from glutamate.[41] The increase in glutamine synthesis abrogates the production of αKG from glutaminolysis, and thus inhibits MTORC1 and enhances autophagy.[39,42] Through a parallel mechanism, MTORC1 is also activated by the energetic input of glutaminolysis through the TTT-RUVBL1/2 complex, which controls the structural stability of MTORC1.[43] In contrast to those observations in mammalian cells, in yeast the synthesis of glutamine rather than glutaminolysis, activates TORC1, following a Gtr1/RRAG-independent mechanism.[44,45] Something similar might happen in *C. elegans*, where αKG addition has been reported to extend life span by inhibiting MTORC1.[46] Altogether, this evidence reveals a pivotal role of glutaminolysis in cancer, linking metabolism and the MTORC1 pathway in order to promote cell growth and anabolism. This link between MTORC1 and glutaminolysis seems to operate in both directions. Indeed, MTORC1 enhances glutaminolysis by activating MYC-GLS and GLUD1, establishing a positive feedback loop that may account for the high consumption of glutamine in cancer cells.[47,48] Therefore, glutaminolysis and MTORC1 mutually regulate each other in order to promote cell growth and cancer progression. In addition to that, the activation of MTORC1 by glutaminolysis also inhibits autophagy and ATM, a protein involved in the DNA damage response (DDR).[40,49-51] Hence, a high rate of glutaminolysis promotes the progression of cancer at early stages, not only stimulating cell growth through the MTORC1 pathway, but also impairing the proper removal of damaged proteins and organelles through the inhibition of autophagy and through ATM-dependent DDR, which eventually would contribute to the initiation of cancer.

Regulation and role of autophagy in cancer cells

During autophagy, cellular components are sequestered into vesicles called autophagosomes and then delivered to lysosomes for degradation (**Fig. 2**). This catabolic process generates both

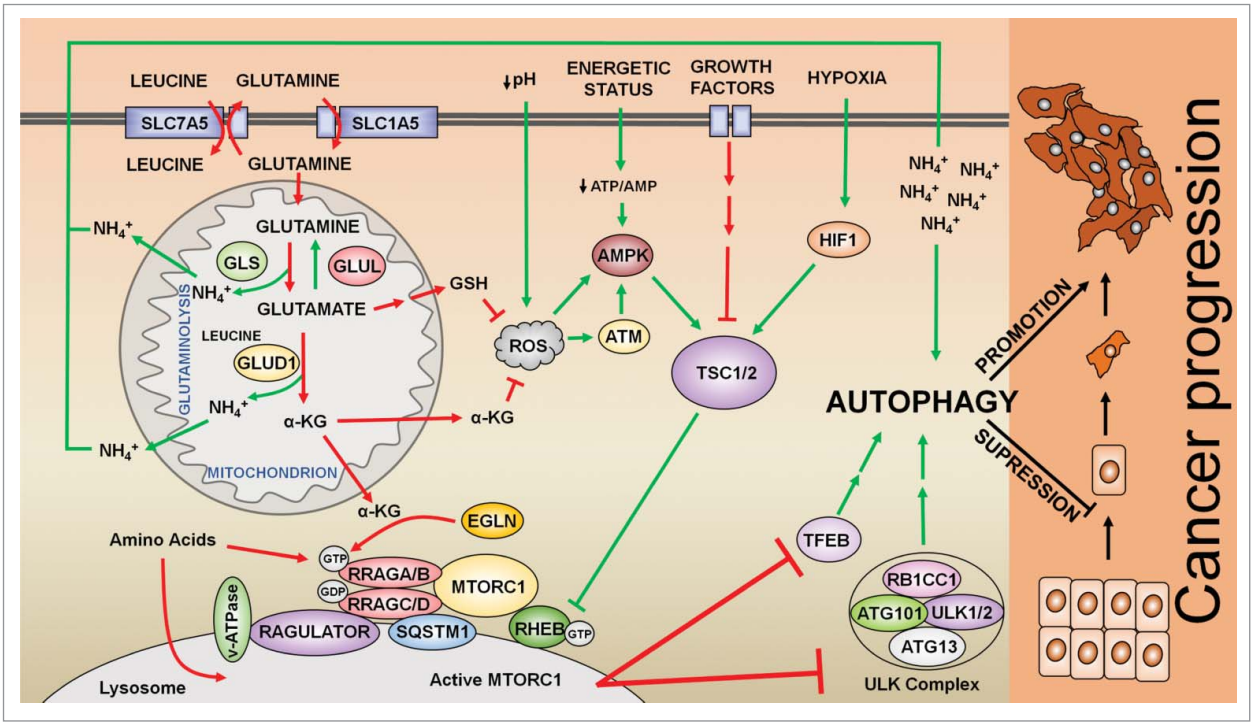

Figure 3. Regulation of autophagy by the MTORC1 signaling pathway in cancer cells. Glutamine is taken up by cells through the transporter SLC1A5. In addition, the antiporter SLC7A5 effluxes glutamine to introduce leucine inside of the cells. Leucine activates GLUD1 (glutamate dehydrogenase 1) allosterically, to promote the production of αKG and the activation of MTORC1 in a EGLN-dependent manner. MTORC1 integrates several inputs, most of them converging in the activation/repression of the TSC1-TSC2 complex, which inhibits RHEB and thus MTORC1. Glutaminolysis activates RRAG proteins, which promote the translocation of MTORC1 to the surface of the lysosome where MTORC1 interacts with its coactivator RHEB. Active MTORC1 induces the phosphorylation of both ULK1 and TEFB to inhibit autophagy. In addition, glutamate, a precursor of GSH (glutathione), along with αKG counteracts ROS levels to inhibit the activation of autophagy mediated by ATM, AMPK, and TSC upstream of MTORC1. Autophagy plays a dual role in cancer: while in early stages autophagy suppresses tumor progression by the removal of damaged cellular components, autophagy promotes the growth and survival of established tumors by providing nutrients and energy at later stages. Green arrows indicate processes that result in autophagy activation; red arrows indicate processes that result in autophagy inhibition.

precursor compounds and energy supply for macromolecular synthesis and metabolic needs. Autophagy is orchestrated by several proteins known as ATG (autophagy-related) proteins through a multistep process that includes initiation and vesicle nucleation, vesicle elongation and fusion, and finally, degradation of the autophagosomal content.[52-54] Upstream of ATG proteins, autophagy is coordinated by several signaling pathways including those that control tumorigenesis.[55,56] Among these pathways, the MTORC1 pathway ensures the regulation of autophagy in response to metabolic and environmental stresses (e.g., nutrients and energy limitation, hypoxia, acidic pH, and oxidative stress) (**Fig. 3**).[57,58] MTORC1 inhibition promotes autophagy by activating the ULK complex, constituted by ULK1/2, ATG13, RB1CC1/FIP200, and ATG101. The active ULK complex phosphorylates BECN1, a key component of the class III phosphatidylinositol 3-kinase complexes (one of which includes PIK3C3, PIK3R4, BECN1 and ATG14), to promote autophagy.[59-61] Upstream of MTORC1, the TSC1-TSC2 complex and the AMPK protein coordinate growth factor and energy signaling cascades.[62,63] In a parallel mechanism, MTORC1 also inhibits autophagy through the phosphorylation and the cytosolic retention of the transcriptional factor TFEB, which controls the expression of genes involved in the execution of autophagy.[64] Although MTORC1 inhibition during nutrient restriction activates autophagy, the reactivation of MTORC1 by recycled nutrients resulting from autophagy is necessary for the restoration of lysosomes and for the termination of autophagy (**Fig. 2**).[65]

Autophagy is primarily a prosurvival adaptive response that enables cells to tolerate unfavorable conditions, including those to which cancer cells are exposed.[16,55,66-70] In response to metabolic stress, caused by limited nutrient and oxygen, autophagy is induced resulting in the degradation of some cellular components and their recycling. This provides nutrients and energy necessary to sustain metabolism; in the case of cancer cells, this ensures tumor growth and survival. In contrast, by virtue of its ability to selectively degrade damaged cellular components, autophagy has been proposed to limit the accumulation of harmful components such as damaged DNA or ROS, thereby preventing tumor initiation. Thus, autophagy plays a dual role in cancer, either suppressing or supporting tumorigenesis, depending on the stage and context of the cancer.

The evidence that autophagy can prevent tumor formation comes from mouse studies in which autophagy is impaired by

genetic manipulation of *Atg* genes. Mice with allelic loss of the essential autophagic gene *Becn1*, with tissue specific knockout of *Atg7*, or with mosaic deletion of *Atg5* have increased susceptibility to development of tumors, in particular those of the liver, relative to wild-type mice.[71-73] In contrast, in advanced stages of tumorigenesis, autophagy may contribute to tumor progression by providing nutrients that allow cell survival under stressful conditions (e.g., oncogene activation, changes in metabolism, hypoxia, ROS accumulation, and acidic pH).[66,67,69,74] Thus, RRAS-induced transformation and tumorigenesis requires autophagy to sustain tumor metabolism and growth.[75] Similarly, $BRAF^{V600E}$-lung driven tumors become addicted to autophagy to sustain mitochondrial glutamine metabolism and tumor growth.[76] Furthermore, the deletion of *Atg5* and *Atg7* causes benign liver adenomas that do not progress to hepatocellular carcinoma, suggesting that autophagy is required for tumor progression into more aggressive stages.[73] Moreover, the expression of the core autophagy gene *MAP1LC3* (a marker of the autophagy process) is increased in samples of aggressive tumors and correlates with the risk of metastatic disease and with a poor patient outcome.[77,78] Autophagy promotes metastasis by limiting detachment-induced cell death (anoikis) during extracellular matrix detachment of cancer cells.[79] Autophagy also contributes to the survival of dormant disseminated tumor cells for extremely prolonged periods.[80] However, although allelic loss of *BECN1* is found in some tumors,[71] the complete deletion of *BECN1* has not been observed, which suggests that BECN1 is necessary for tumorigenesis and for the maintenance of the malignant state.[81]

Mechanistic link between glutaminolysis and autophagy

Mortimore and Schworer in 1977 provided the first evidence that amino acids regulate autophagy, observing that amino acid deprivation induces the accumulation of autophagosomes in perfused rat liver.[82] Thereafter, Blommaart et al.[83] in 1995 showed that the effect of amino acids on autophagy is mediated by MTOR (mechanistic target of rapamycin). MTOR is an atypical serine/threonine kinase that integrates several stimuli to regulate metabolic and signaling pathways.[17,84] MTOR exists as 2 structurally and functionally different complexes, termed MTORC1 and MTORC2.[19,84] Whereas the activation of MTORC2 is modulated mainly by growth factors, MTORC1 integrates different input cues such as growth factors, energetic status of the cell, oxygen and nutrients. Most of the upstream inputs that signal toward MTORC1 are integrated by the TSC complex, which ultimately regulates RHEB activation upstream of MTORC1 (**Fig. 3**). In contrast, amino acids activate MTORC1 via another family of small GTPases known as RRAG. Amino acid addition activates RRAG and promotes the translocation of MTORC1 to the surface of the lysosome, a process in which SQSTM1/p62, a protein involved in autophagy as well as other processes, also participates.[85,86] Once at the surface of the lysosome, MTORC1 is activated through its direct interaction with the coactivator RHEB (**Fig. 3**).[19,84]

Although the mechanism by which MTORC1 senses amino acids is complex and not completely understood,[18,19] MTORC1 can detect the presence of glutamine and leucine through glutaminolysis.[12,40,87] Thus, the production of αKG through glutaminolysis activates MTORC1 and hence, inhibits autophagy. The activation of MTORC1 exerted by αKG occurs via an increase in the GTP loading of RRAGB (a member of the RRAG family), which permits the translocation of MTORC1 to the lysosome surface, and its subsequent activation.[12] The activity of EGLNs/prolyl hydroxylases is crucial for this αKG-dependent activation of MTORC1. EGLNs are the oxygen sensors of the cell, that require both oxygen and αKG to hydroxylate target proteins (such as hypoxia inducible factors).[88] However, in normoxic conditions, when oxygen is not limiting, EGLN activity strictly depends on intracellular αKG levels. Therefore, at a high glutaminolytic rate, increased levels of αKG activate EGLNs, which, in turn, promotes MTORC1 activation and the subsequent inhibition of autophagy. Thus, EGLNs constitute a mechanistic link between αKG production and MTORC1 activation.[40] However, the interaction between glutaminolysis and MTORC1/autophagy seems to be more complex. A recent report suggests that αKG activates MTORC1 and inhibits autophagy through a parallel mechanism involving acetyl-CoA synthesis and protein acetylation.[89] Furthermore, despite the inhibitory effect of glutaminolysis on autophagy, the by-product of glutaminolysis, ammonium, has a dual role in autophagy, activating this process at low concentrations (2–4 mM), and inhibiting autophagy at higher concentrations.[90] This observation, however, differs from previous observations by Seglen et al., who showed that at least in hepatocytes ammonium, known to increase the intralysosomal pH, cannot activate autophagic flux, even at low concentrations.[91] Although the mechanism by which ammonium induces autophagy remains largely undescribed, it seems to be independent of MTORC1-ULK.[92]

Another interesting molecular connection between glutaminolysis and autophagy is related to ROS production. The accumulation of ROS activates autophagy through mechanisms that affect both the core autophagy machinery and the components of signaling pathways that regulate autophagy.[93,94] Several ATG proteins are redox sensitive. One well-known example is ATG4: when oxidized by ROS, ATG4 prevents the delipidation of the autophagy marker MAP1LC3, thus leading to sustained autophagy.[95] ROS indirectly regulates autophagy by promoting activation of AMPK and MAPK8/JNK1, leading to the inactivation of MTORC1 and the disruption of the BECN1-BCL2 complex, respectively.[96–98] ROS may also activate autophagy through the activation of ATM, a kinase that plays a key role in DDR. In turn, active ATM inhibits MTORC1 through the AMPK-TSC-RHEB axis.[99] Moreover, under hypoxia, autophagy is induced through a ROS-dependent mechanism. This form of autophagy is activated through 2 distinct mechanisms: the hypoxia-inducible, factor-mediated induction of BNIP3 and BNIP3L proteins, and the activation of AMPK.[100,101] Conversely, some oxidative agents inhibit autophagy by inactivating proteins that regulate autophagy, such as the TSC complex.[102] Whether the regulation exerted by ROS on autophagy is dependent on the nature or the duration of oxidative stress is still unknown. Interestingly, glutaminolysis intermediates cooperate in the production of the antioxidants GSH and NADPH.[10] Furthermore, αKG reacts nonenzymatically with ROS (**Figs. 2, 3**).[103,104] Therefore, in addition to its effects on MTORC1, glutaminolysis inactivates

autophagy by counteracting the production of ROS and increasing the levels of GSH, NADPH, and αKG. The link between ROS and glutaminolysis is supported by the observation that the inhibition of either GLUD1 or GLS2 leads to an increase in ROS levels.[87,105] As glutamate produced by GLS sustains the synthesis of GSH, the inhibition of GLS decreases the levels of GSH and the ability of cells to counteract ROS.[105,106] Similarly, a decrease in levels of GLUD1 augments the levels of ROS, probably due to a decrease in the production of NADPH and αKG.[36,87] Hence, glutaminolysis counteracts the constant oxidative stress to which cancer cells are exposed.[107] This, together with the advantages provided by glutaminolysis to cancer cell growth (including MTORC1 activation), renders this enzymatic process an interesting therapeutic target.

Despite the fact that MTORC1 activation represses autophagy, autophagy is also upregulated in MTORC1 hyperactive tumors (e.g., TSC1-TSC2 tumors).[62] One mechanism proposed to explain this observation relies on the influence of the microenvironment of tumor cells. Indeed, a body of evidence suggests that autophagy is induced in cancer cells by microenvironmental stresses including growth factor withdrawal (through MTORC1 inhibition), hypoxia (through hypoxia inducible factor stabilization), oxidative stress (through ROS), and acidic pH (through AMPK activation and MTORC1 inhibition).[69,108,109] The tumor cell microenvironment influences the regulation of autophagy and energy metabolism not only in cancer cells but also in stromal cells. Thus, the accumulation of ROS in the microenvironment of the tumor cell promotes autophagy in surrounding stromal cells, leading to an influx of nutrients (including glutamine) from stromal cells to cancer cells.[69] Subsequently, glutamine provided by stromal cells is metabolized by the cancer cells through glutaminolysis. As explained above, ammonium produced as a by-product of glutaminolysis may diffuse into the tumor cell microenvironment and amplify autophagy in stromal cells, facilitating tumor growth by providing metabolic and energy substrates to cancer cells.[90] This positive feedback between stromal cells and cancer cells is a vicious circle that enables cancer cells to survive at the expense of stromal cells.[90,92] As glutaminolysis on the one hand inhibits autophagy through the activation of MTORC1, and on the other hand stimulates autophagy by producing diffusible ammonium, it remains to be determined how autophagy is switched on or off in response to glutaminolysis in cancer cells. The elucidation of these mechanisms might provide new therapeutic strategies for targeting autophagy and glutaminolysis in tumor cells.

Targeting glutaminolysis and autophagy as an anticancer therapy

Several oncogenes and tumor suppressors regulate the activity of MTORC1, thus the overactivation of this pathway is commonly detected in cancer (80% among all the different types of cancer).[110] Therefore, the inhibition of MTORC1 was considered as a potential strategy to treat cancer. However, clinical trials using different analogs of rapamycin, (CCI-779, RAD001, AP23573) have shown only modest effects in patient outcome, with promising results only for a few types of tumors, particularly mantle cell lymphoma, endometrial cancer, and renal cell carcinoma.[111,112] Although the unsuccessful results obtained with rapamycin analogs have been explained in part by their inability to inhibit MTORC2, the treatment of lymphoblastic leukemia with PP242 (a dual inhibitor of both MTORC complexes) displays similar effects as rapamycin treatment.[113] Therefore, the lack of inhibition of MTORC2 does not seem to explain the limited effect of rapamycin analogs against cancer. Alternatively, the negative feedback loop connecting MTORC1 and IRS1 increases the activation of the AKT/PKB pathway upon MTORC1 inhibition, promoting cell survival. This negative feedback loop might explain partially the lack of effectiveness of rapamycin treatment.[114-116] Also, the MKNK1/Mnk-EIF4E and MAPK/ERK-RPS6KA3/RSK2 pathways participate in the resistance to rapamycin analogs.[112] Finally, as we will discuss below, MTORC1 inhibition leads to autophagy activation, which permits the survival of cancer cells.

Currently the metabolism of cancer cells has been rekindled as a therapeutic target against cancer. An increasing number of reports are describing the mechanism by which oncogenes and tumor suppressors modulate metabolic pathways which are relevant for cancer cell growth.[11] The link established between glutaminolysis and MTORC1 partially accounts for glutamine addiction in cancer cells.[12,42,87,117] Therefore, targeting glutaminolysis, which is a process that both activates MTORC1 and provides substrates for the anabolic machinery led by MTORC1, is a rational therapeutic approach to target simultaneously metabolism and cell signaling in tumors. A logical conclusion from this connection is that the inhibition of MTORC1 can be addressed by inhibiting either the enzymes of glutaminolysis (GLS and GLUD1), or the intermediates between glutaminolysis and MTORC1, such as the EGLNs.[40] Indeed, the inhibition of glutaminolysis as a cancer therapy has been considered for many years.[24] Unfortunately, this strategy has not yet led to successful results. One limitation of targeting GLS as a cancer therapy is that GLS is not only required for metabolism in cancer cells, but also for the development, growth, maintenance, and physiology of normal tissues (e.g., enterocytes, glutamatergic neurons, renal ammonium excretion). Thus, inhibiting glutaminolysis might result in serious complications in the patient. Indeed, early preclinical studies with DON (6-diazo-5-oxy-L-norleucine) and with 2 other glutamine mimetic compounds (azaserine, acivicin) showed limited antitumor effects and severe toxicity (nefrotoxicity, gastrointestinal toxicity and myelosuppression).[5,118] In addition, other compounds such as BPTES (an allosteric inhibitor of GLS), and 968 (an inhibitor of Rho GTPase), have been described. Although these compounds exhibit both an increased specificity against GLS isoforms and antitumor effects on several cancer cell lines, their hydrophobic nature has hindered their application in vivo.[9,24] In contrast, a recent promising inhibitor of GLS has been described, CB-839, which is currently being tested in clinical trials against several types of tumors.[119] The second enzyme of glutaminolysis, GLUD1, is another interesting target for cancer therapies. EGCG, an allosteric inhibitor of GLUD1, has earned attention as a putative therapeutic agent, with significant antitumor effects in preclinical studies.[120] Of

note, EGCG treatment leads to glucose addiction in vitro, sensitizing the cells to glucose withdrawal. Thus, EGCG treatment might synergize with therapies that target glucose metabolism.[121] However, the antitumor mechanism of EGCG has not been clearly related with its ability to inhibit GLUD1.[122]

Another interesting option to decrease MTORC1 activity could be the inhibition of EGLNs, which links glutaminolysis with MTORC1 activation. Interestingly, several molecules able to inhibit EGLNs are currently being evaluated in clinical trials for the treatment of anemia (FG-2216, FG-4592, GSK1278863A, and AKB-6548).[123] As EGLNs are well-known activators of hypoxia inducible factor degradation, an important limitation in the use of EGLN inhibitors in the treatment of cancer would be the activation of the hypoxic response mediated by hypoxia inducible factors.[88,124] However, human cells present 3 different isoforms of EGLNs (EGLN1/PHD2, EGLN2/PHD1 and EGLN3/PHD3), and only EGLN1 seems to be physiologically involved in the regulation of hypoxia inducible factor signaling.[125] Of note, EGLN3 interacts with SQSTM1/p62, suggesting a direct link with MTORC1 activation.[85,88,126] EGLN3 has also been related with apoptosis and tumor suppression.[127] Therefore, the selective inhibition of each isoform of the EGLN family is an interesting field to explore potential anticancer therapies. Hence, EGLNs are hubs where several cellular processes converge, constituting a highly interesting target against cancer.

As stated above, autophagy is upregulated in many established cancer cell types.[75] Furthermore, autophagy may be activated in tumor cells in response to a variety of anticancer therapies.[128-131] Autophagy confers resistance to therapy, and the inhibition of autophagy sensitizes tumor cells to cell death induced by several anticancer treatments.[129] In the presence of certain anticancer agents, however, the induction of autophagy results in synergistic antitumor effects.[130,131] Thus, autophagy can be considered as a double–edged sword in tumorigenesis and cancer therapy. Given the important functions of autophagy in cancer, a number of clinical trials have investigated the effect of modulation of autophagy for the treatment of tumors.[132,133] Thus, the autophagy inhibitor hydroxychloroquine is being evaluated currently in phase I-II trials in combination with anticancer therapies (https//clinicaltrials.gov/).[132,133] Although the inhibition of MTORC1 abrogates anabolism and cell growth, it also promotes the activation of autophagy and, as a consequence, the survival of tumor cells. Whereas the inhibition of MTOR and MTOR-activating mechanisms (such as glutaminolysis) presents several limitations as anticancer monotherapies, a combined therapy targeting both MTORC1 and autophagy may improve treatment outcome. Indeed, preclinical and clinical experiments have shown that the combination of MTORC1 and autophagy inhibitors display synergistic effects.[132,134,135] Therefore, to prevent cancer cell survival and metastatic disease, the inhibition of either glutaminolysis or EGLNs might require the concomitant inhibition of autophagy.

The inhibition of MTORC1 also sensitizes cancer cells to DNA damaging agents such as melphalan, AraC, etoposide and ionizing radiation.[113,136-138] The mechanism that explains this observation is related to the ability of MTORC1 to regulate the expression of FAN1/FANCD2, a protein involved in the activation of ATM. Thus, the inhibition of MTORC1 decreases FAN1, which impairs the activation of ATM and thereby the DDR of cancer cells.[113,136,139] Furthermore, AMPK is another link between ATM and MTORC1, as AMPK regulates both ATM and MTORC1.[50,51,140-142] Those results highlight the potential synergy of a combined therapy targeting both MTOR and DDR as a better strategy to prevent tumor resistance to chemotherapeutic agents.

Conclusion

The high consumption of glutamine is a well-known metabolic feature that provides several advantages to proliferating cancer cells. Through glutaminolysis, glutamine modulates both the activation of MTORC1 and the inhibition of autophagy. Thus, although the inhibition of glutaminolysis leads to an inhibition of MTORC1, it would also promote the activation of autophagy, which is crucial for the survival of cancer cells. Therefore, the simultaneous inhibition of both glutaminolysis and autophagy may display a synergistic effect that could improve patient outcome with lower toxicity and side effects. This therapeutic strategy could be particularly valuable in patients with tumors that consume high quantities of glutamine. Although several inhibitors of glutaminolysis have been described, the lack of specificity has hindered their path to become antitumor agents. Hence, given the high relevance of glutaminolysis for cancer cells, the rational design of new inhibitors of glutaminolysis, along with improved autophagy inhibitors, are required to provide better therapeutic options against cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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