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Autophagy: a targetable linchpin of cancer cell metabolism

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Abstract

Cancer cells display several features of aberrant cellular metabolism. Two consequences of this dysregulated metabolism are rapid depletion of intracellular nutrients and a buildup of aggregated proteins and damaged organelles. Autophagy provides a mechanism for recycling proteins, lipids, and organelles. In cancer cells, oncogenes and conditions of severe stress drive profound upregulation of autophagy. In this setting, autophagy ameliorates the ill effects of dysregulated cellular metabolism, allowing a steady supply of nutrients and removal of damaged organelles. Although therapeutic strategies targeting cancer cell metabolism and autophagy are already entering clinical trials, further study of the precise mechanisms of interplay between oncogenic signaling, cellular metabolism, and autophagy will provide more effective strategies in the future.

Dysregulated autophagy is emerging as a hallmark of malignancy

Over the past several decades significant advances have been made in understanding how aberrant growth factor signaling, as well as genetic and epigenetic changes, promote a form of cellular metabolism that enables the self-sufficient, hyperproliferative state we associate with malignancy. Although the metabolic underpinnings of malignant transformation were heralded almost a century ago with Otto Warburg's observation that proliferating tumor cells consume glucose and produce lactate at supranormal rates, several new features of metabolic transformation have recently emerged [1,2]. In addition to a reliance on aerobic glycolysis (i.e., the 'Warburg Effect'), some of these emerging 'metabolic hallmarks' of malignancy include increased rates of glutamine catabolism, *de novo* fatty acid and lipid synthesis, and anaplerosis [3]. Oncogenes, mutated tumor-suppressor genes and cancer-specific metabolic isozymes each have profound regulatory effects on cellular metabolism [4,5]. Ultimately cancer cells obtain a selective advantage due to their metabolic dysregulation, but at the same time are handcuffed by a relentless biosynthetic demand. As such, they are required to mitigate the harmful effects of the byproducts of unbridled growth and proliferation, such as reactive oxygen species (ROS), as well as procure metabolic building blocks to fuel accelerated biosynthesis. Such accommodation is required irrespective of the limited extracellular nutrient supply that frequently accompanies disordered tumor tissue growth. Because of its prominent role in achieving this accommodation, autophagy (see Glossary) is

beginning to be understood not only as a consequence of malignant transformation, but also as a metabolic hallmark in and of itself.

Autophagy is an intracellular recycling program that, under physiologic circumstances, responds to nutrient, energy, oxygen, and hormonal demands to maintain metabolic homeostasis [6]. It plays a crucial role during cellular conditions of stress and starvation. In periods of nutrient deprivation, autophagy allows for lysosomal degradation of organelles, cytoplasmic proteins, and lipids to produce amino acids, fatty acids, and acetyl-CoA in support of cellular biosynthesis and energy demands [3]. Mitochondrial health – which, as a potential source of ROS and death signals, can dictate life and death in a stressed cancer cell – is maintained by autophagy through the removal and recycling of damaged mitochondria (‘mitophagy’) [4,7]. Chemotherapeutic agents may further induce alterations in cell signaling and metabolism, thereby activating cellular stress resistance mechanisms such as autophagy [8,9]. The profound dysregulation of cancer cell metabolism found during tumorigenesis and during treatment, and the subsequent reliance on autophagy to adapt to such dysregulation, are providing new molecular targets for cancer therapy [5,10]. The subject of this review is the interplay between altered cellular metabolism and autophagy in the context of malignancy.

The role of autophagy as a survival pathway in cancer

The tumor microenvironment is metabolically challenging, and cancer cells survive by relying on a variety of intracellular stress response systems. One such response is autophagy. Autophagy is, in essence, an intracellular recycling program, whereby organelles, cytoplasmic proteins, protein aggregates, and lipids are delivered to lysosomes for catabolic breakdown to molecular building blocks that may be reused by the cell for energy and macromolecular synthesis. Breakdown of these structures can function as an essential homeostatic process (‘basal autophagy’) [10] – recycling damaged organelles and misfolded protein aggregates – or as a response to stresses such as nutrient deprivation, hypoxia, intracellular pathogens, or chemotherapy (‘stress-induced autophagy’) [10]. Although the homeostatic role of basal autophagy may function as a tumor-suppressive mechanism in particular contexts (Box 1), the autophagic machinery appears to be hijacked in developed tumors to support dysregulated metabolism.

A series of evolutionarily conserved protein complexes coordinate the formation of autophagosomes. A complete review of the molecular process involved in autophagy has been previously described [10]. Briefly, autophagy is orchestrated by five major complexes or steps: (i) Unc-51-like kinase (ULK1) complex, which serves as the liaison between growth factor signaling, nutrient sensing, and downstream autophagy complexes; (ii) the Beclin1-vacuolar sorting protein (VPS34) complex which is responsible for nucleation of the initial autophagosomal membrane from the endoplasmic reticulum (ER) and other sources of membrane; (iii) the ATG cascade of enzymes that serves to expand the autophagosome and recruit cargo; (iv) autophagic vesicle–lysosome fusion; and (v) degradation of autophagic vesicle cargo and recycling of nutrients and macromolecules, as illustrated in Figure 1.

Although persistent autophagy can lead to cell death, unlike cells committed to apoptosis or necrosis, highly autophagic cells that survive a stress can clear autophagic vesicles rapidly and resume exponential growth once the stress is removed. This reversible nature of autophagy allows cells to use this catabolic process as a survival mechanism [11]. Autophagy promotes survival in cancer cells by providing an internal source of nutrients in times when external nutrients are limited. Mitophagy can mitigate the oxidative stress that is engendered by leaky mitochondria and sequester mitochondria, possibly limiting cytochrome *c* release and progression of caspase-induced apoptosis [12]. Autophagy rids the cell of oncogenic p62 [13], and of misfolded, oxidized, and aggregated proteins that cannot be degraded by the proteasome [14]. Evidence suggests that autophagy plays a role in proper secretion of extracellular proteins [15], as well as in the disassembly of the mitotic spindle apparatus following cell division [16]. Despite earlier evidence that allelic loss of one copy of the autophagy gene *BECN1* (Beclin 1) (found in several malignancies) may downregulate autophagy, and thereby promote tumorigenesis at the onset of oncogenic transformation [17], evaluation of human cancer specimens from advanced solid tumors of multiple histologies found that very high expression of LC3 – a key autophagosomal modulating protein – was a near-universal phenomenon [18]. Even in highly glycolytic tumors (e.g., melanoma) that appear to be replete with nutrient on [¹⁸F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, high levels of autophagy can be measured [19], reflecting the crisis-like conditions engendered by oncogenic transformation.

Oncogenic kinases, metabolic enzymes, and autophagy

Several metabolic pathways are constitutively activated in cancer cells, most notably those of aerobic glycolysis, glutaminolysis, *de novo* synthesis of fatty acids and lipids, and anaplerosis. Upregulation of these enzymatic pathways is driven either by cancer-specific isoforms of metabolic enzymes such as pyruvate kinase M2 isoform (PKM2), lactate dehydrogenase A (LDHA), pyruvate dehydrogenase kinase 1 (PKD1), and hexokinase 2 (HK2), or by mutated or aberrantly activated oncogenes – which influence metabolic pathways – or both [3,5].

Two major growth factor-responsive pathways, the phosphoinositide 3-kinase (PI3K), AKT/protein kinase B, mammalian target of rapamycin (mTOR) pathway and the mitogen-activated protein kinase (MAPK) pathway, are frequently mutated or aberrantly activated in human cancers. These pathways also have profound on cellular metabolism that help drive cells toward a malignant phenotype. Indeed, activation of the PI3K/AKT/mTOR pathway upregulates nutrient transporters, amplifying cellular uptake of amino acids, glucose, and other nutrients [20]. AKT activation induces changes in gene expression that allow increased glycolysis and lactate production, as well as inhibition of fatty acid oxidation [21,22]. Activation of the PI3K/AKT/mTOR pathway is also known to upregulate lipid [23] and protein macromolecule synthesis [24]. PI3K pathway activation is associated with increased expression of the transcription factor MYC and stabilization of hypoxia-inducible factor-1 α (HIF1 α) [25,26]. These two oncogenes cooperatively regulate the transcription of several key metabolic isozymes in cancer cells (i.e., the glucose transporter GLUT1, HK1/HK2, LDHA, PDK1) and thus play a role in driving aerobic glycolysis (Figure 2) [27–30].

Activation of MYC is also known to upregulate glutamine catabolism. Glutaminolysis provides highly proliferative cancer cells with: (i) a source of nitrogen for amino acid and nucleotide synthesis, (ii) citrate for lipid synthesis, (iii) carbon units to maintain tricarboxylic acid cycle (TCA cycle) intermediates and oxidative phosphorylation (anaplerosis), and (iv) NADPH for lipid and nucleotide biosynthesis [4]. Cells overexpressing MYC have been reported to be addicted to glutamine for survival [31].

Mutations in the MAPK signaling pathway, specifically the RAS family of oncogenes, also have profound effects on cellular metabolism. Activated forms of RAS (both directly and through activation of HIF1 α) are known to diminish the acetyl-CoA pool and cause depletion of TCA cycle metabolites citrate and isocitrate [32]. RAS also activates the PI3K pathway and inhibits mitochondrial uptake and processing of fatty acids by β -oxidation [33]. Activating mutations in RAS pathways have been shown to produce elevated rates of autophagy and mitophagy even when nutrients are in good supply. This can be effected through several MEK/ERK-mediated mechanisms, including upregulation of Beclin1 and induction of Noxa [which displaces Beclin1 from myeloid leukemia cell differentiation protein (MCL-1) and promotes autophagy], or through expression of BCL-2/adenovirus E1B 19K-interacting protein 3 (BNIP3) [which competes with B cell lymphoma protein (BCL-2) binding to Beclin1 and induces autophagy] [34,35].

Much of this metabolic rewiring is integrated via the mitochondria. Whereas aerobic glycolysis tends to shunt pyruvate away from the mitochondria and oxidative phosphorylation processes, concurrent glutaminolysis (which largely takes place in the mitochondria) provides carbon units to maintain the TCA cycle and allow oxidative phosphorylation to persist [36,37]. In addition, reductive carboxylation enabled through glutaminolysis in the mitochondria provides an important source of citrate, which can be exported to the cytosol for lipid synthesis [38,39]. Furthermore, under hypoxic tumor conditions, ROS are generated by mitochondrial complex III and trigger HIF1 α signaling leading to further metabolic dysregulation [40]. In the oncology setting it is important to recognize the role the mitochondria play in initiating apoptosis. In a teleological sense, as cellular stress and altered metabolism persist and are sensed at the mitochondria, programmed death pathways are initiated as an attempt to preserve the health of the tissue or organism as a whole. In opposition to this, cellular stress and oncogenic signaling may enlist autophagy as a cellular survival mechanism, preserving aberrant homeostasis (Figure 2).

Byproducts of cancer metabolism, such as ammonia [41], ROS [42], oxidized proteins [43], aggregated proteins [43], hypoxia [44,45], and increased AMP/ATP ratio [46] are all known triggers of autophagy. In this setting, autophagy plays two crucial roles in allowing the cell to avert death: (i) it provides a supply of energy, metabolic intermediates, and macromolecular raw materials for supporting growth and division; (ii) it recycles toxic and damaged organelles such as mitochondria, controlling generation of ROS and subsequent triggering of ROS-induced necrosis or mitochondrial initiated apoptosis (Figure 2) [47,48]. Demonstrative of this are studies of murine cell lines that have been genetically altered to overexpress H-Ras or K-Ras. Basal autophagy was typically estimated to have increased by 10-fold in these cells. However, when the autophagy machinery was dismantled by deletion of essential autophagy genes, these cells show a pronounced accumulation of dysfunctional

mitochondria [32]. The consequences on mitochondrion-mediated metabolism were significant, including citrate depletion, dysfunctional TCA cycling, and inhibition of oxidative phosphorylation [32].

Autophagy activation in response to overexpression of oncogenes such as MYC [49] or RAS [34] seems to function as a host-protective mechanism, digesting cellular contents and either promoting senescence [50] or inducing a catabolic cell death [34], thus limiting the potential for oncogenic transformation. However, in the setting of multiple, simultaneous oncogenic mutations, autophagy seems to be enlisted as a support mechanism for unlimited growth and proliferation (Figure 3). Metabolic stress sensors, some of which play intimate roles in oncogenic signaling, are key regulators of autophagy's double-edged sword.

Metabolic stress sensors regulate autophagy

Because autophagy has tremendous destructive potential, the cell has multiple means of achieving fine-tuned and dynamic control of autophagy. Mammalian target of rapamycin complex 1 (mTORC1), AMP-activated protein kinase (AMPK), and the ER stress response comprise the three best-characterized metabolic stress sensors that directly regulate autophagy and link the autophagic stress response to growth factor signaling, cellular energy balance, and cellular protein metabolism.

mTORC1

mTORC1 functions as a master regulator of cellular growth and proliferation. Several members of the PI3K/AKT/mTOR signaling pathway are commonly mutated in human cancers and function as inducers of mTORC1 activity. At the same time, several tumor-suppressor genes that are commonly inactivated in cancer – such as phosphatase and tensin homolog (PTEN), tuberous sclerosis complex 1/2 (TSC1/TSC2), neurofibromin 1/2 (NF1/NF2), and liver kinase B1 (LKB1) – function as crucial inhibitors of mTORC1 activity. Thus, oncogenic transformation and unchecked mTOR activity are often closely coupled. In a general sense, mTORC1 activation promotes growth and proliferation while generally dampening autophagy, whereas mTORC1 inhibition curtails growth and disinhibits autophagic activity [51].

mTORC1 activity is most directly affected by its interaction with the lysosome-bound GTPase Ras homolog enriched in brain (RHEB) [52]. This interaction is primarily regulated by two distinct mechanisms: (i) growth factor (e.g., AKT, ERK1/2) regulation of the TSC1/2 complex and (ii) amino acid-dependent recruitment of mTORC1 to the lysosome. Regarding this second level of control, two pairs of Rag GTPases, held in place within mTORC1 by the Regulator complex, are activated by elevated amino acid concentrations and subsequently usher mTORC1 to the lysosome, allowing close proximity to RHEB [53]. Inactivation of the Regulator complex has been shown to block amino acid signaling to mTORC1 [54]. Although the precise mechanism of amino acid sensing is unknown, it appears that MAP4K3 and vacuolar sorting protein (VPS34) may have important roles [55,56]. Interestingly, VPS34 is also known to have an important role in autophagy, and thus may provide a molecular link between assembly of the autophagosome and amino acid sensing.

mTORC1 is also a master regulator of autophagy. In nutrient-replete conditions, activated mTORC1 phosphorylates the ULK1 and ATG13 components of the ULK1–ATG13–FIP200–ATG101 kinase complex, inhibiting its activity and thus blocking autophagy induction [51,57]. The downstream mTORC1 effectors, MYC [58] and HIFs [59] (in addition to their roles in oncogenic metabolic reprogramming) also have important roles in autophagy induction (Figure 2).

AMPK

Within the PI3K pathway, the LKB1–AMPK pathway is also an important regulator of autophagy. Serving as a messenger of low intracellular ATP levels to the autophagic machinery, LKB1–AMPK is an energy-sensor pathway that activates autophagy through multiple pathways, including p70 stabilization [60] and inhibition of mTORC1 (Figure 2). AMPK has also been shown to directly phosphorylate ULK1, a kinase complex critical for the initiation of autophagy (Figure 1) [61]. Through ataxia telangiectasia mutated (ATM), AMPK signaling also activates autophagy in response to rising intracellular concentrations of ROS [62]. AMPK may also be a link between the DNA damage response and autophagy induction because cytoplasmic p53 and activated ATM induced by DNA damage may activate autophagy through AMPK- and mTORC1-dependent mechanisms [63–65].

ER stress response

Autophagic flux is also responsive to metabolic damage, principally signaled through the ER stress response. ER stress has been shown to activate autophagy in both yeast and mammalian cells [66]. An excess of misfolded or unfolded proteins in the ER lumen triggers the stress response through three sensors: protein kinase RNA-like ER kinase (PERK), inositol-requiring transmembrane kinase/endonuclease 1 (IRE1), and activating transcription factor 6 (ATF6α) [58,67]. MYC overexpression has also been shown to activate the ER stress response, followed by PERK-mediated processing of LC3 (a key protein in autophagosomal expansion) and induction of autophagy [58]. The role of IRE1 and ATF6α in autophagy upregulation is less well studied. Recent evidence indicates there is increased crosstalk between the ER stress response and mTOR signaling [68], underscoring the long-understood view of the ER stress response as an intricate, multifaceted nutrient sensor that is designed to protect protein homeostasis in the face of extreme nutrient limitations or overabundance.

Autophagy and metabolic stress in cancer

In addition to the effects of dysregulated kinase signaling and energy stress sensors on autophagy, the direct effects of specific nutrient deficits and metabolite excesses in malignancy underscore the role of autophagy as a linchpin of metabolic reprogramming. Substrate limitation is a crucial regulator of autophagy, especially in the setting of relentless biosynthetic demand placed on the cell by activated oncogenes. Oxygen, glucose, and amino acid deprivation are each strong promoters of autophagy. It is known that normal cells grown in hypoxic conditions (1% pO₂) as well as hypoxic tumor cells show markers of increased autophagy [44]. The effects of hypoxia in this regard are largely mediated through HIFs. Under hypoxic conditions HIF subunits are stabilized, gain entry to the nucleus, and

therein regulate hypoxia-induced gene expression [69]. HIF-dependent upregulation of BNIP3 induces mitochondrial selective autophagy in this way [42]. HIFs also regulate autophagy indirectly through negative feedback on mTORC1 activity via TSC1/2 activation (Figure 2) [70].

Glucose deprivation also induces autophagy [71]. In response to changes in AMP and ADP concentrations in the setting of glucose deprivation, AMPK is activated by LKB1. Autophagy is subsequently upregulated through both mTORC1-dependent and independent mechanisms. Specifically, AMPK, activated by limiting conditions, inhibits mTORC1 through phosphorylation of the tumor-suppressor TSC2, as well as through phosphorylation of an mTORC1 subunit known as regulatory associated protein of mTOR (Raptor) [46]. Independently of mTORC1 inhibition, the LKB1–AMPK pathway is also known to activate autophagy by phosphorylation of ULK1 (Figure 2) [61]. In addition, glucose deprivation is one of the most potent inducers of ER stress-associated autophagy [72].

Through mTORC1-dependent and independent mechanisms, amino acid deprivation is a profound inducer of autophagy. Amino acid replete conditions are a necessary requirement for localization of mTORC1 on the lysosomal membrane, which may allow effective inhibition of autophagosome–lysosome fusion. In conditions where amino acids are limiting, mTORC1 remains unassociated with the lysosome and inhibition of autophagy is withheld [54]. Autophagy is also induced in an mTORC1-independent fashion by ammonia generation, a critical byproduct of glutaminolysis, also upregulated in malignant cells (Figure 2) [8,41]. In addition, indirect evidence that autophagy supplies submillimolar levels of glutamine to cells was recently demonstrated by investigators studying metabolic flux in *Atg5^{-/-}* and *Atg5^{+/-}* mouse embryonic fibroblasts (MEFs) [73].

Sugar transport across the lysosomal membrane also appears to exert significant influence over the autophagic machinery. It has been shown that a lysosomal efflux permease, Spinster (Spin), is required for autophagic lysosome formation following starvation-induced autophagy. Remarkably, it is the sugar transporter activity of Spin, in addition to mTOR kinase activation, that is the essential component enabling this transformation [74]. The discovery of Spinster represents the first direct evidence of autophagic recycling of nutrients.

Regarding lipid metabolism, autophagic regulation of cholesterol may have relevance to tumorigenesis through activity of wild type P53-induced phosphatase (WIP1). It has been shown that WIP1, in addition to emerging as a potent regulator of tumorigenesis (through regulation of ATM and P53), is an important regulator of autophagy-dependent cholesterol efflux, especially in macrophages and developing foam cells [75]. Further work is needed to determine if this is also the case in cancer cells.

Autophagy and the tumor microenvironment

Recent work has implied a developing model of metabolic interaction between cancer cells and stromal cells in their microenvironment, as well as between cancer cells themselves. In this model, cancer cells are theorized to induce autophagic catabolism in adjacent fibroblasts, allowing a crucial supply of nutrients. This is proposed to occur through

induction of oxidative stress in cancer-associated fibroblasts that leads to upregulation of HIF1 α and NF- κ B, activating autophagy and mitophagy, as well as promoting aerobic glycolysis [76]. These events as a whole are proposed to allow the supply of amino acids and high-energy substrates such as lactate and pyruvate to flow from surrounding fibroblasts to metabolically challenged cancer cells. It has been suggested that high autophagy rates observed in cancer cells are an artifact of *in vitro* study, which isolates cancer cells from the tumor microenvironment. It is further suggested that, because autophagic processes in cancer-associated fibroblasts supply cancer cells with glutamine, ammonia generated in malignant cells through subsequent glutaminolysis induces higher levels of autophagy in the fibroblasts [76]. In further evidence of tumor-related metabolic symbiosis, recent reports have noted evidence of two distinct metabolic compartments within the microenvironment of breast cancer tissue: a mitochondria-rich compartment of epithelial cancer cells and a mitochondria-deficient population of glycolytic stromal cells [77,78]. Many aspects of this proposed metabolic model of parasitism in cancer tissue remain to be verified.

Therapeutic forefronts

The unique metabolic characteristics and alterations in autophagic flux of malignant cells have led to several promising targets for therapeutic intervention. Metabolic targets have mostly centered on the distinct elements of glucose metabolism in cancer cells, in other words aerobic glycolysis. Compounds targeting glucose transporters HK2, PKM2, LDHA, and PDK are being actively investigated in clinical studies and appear to have synergistic effects in combination with conventional chemotherapy or radiotherapy [5]. In clinical studies targeting autophagy, chloroquine derivatives have shown promise in advanced solid tumors such as melanoma [10] and glioblastoma multiforme [79]. These compounds, including hydroxychloroquine, inhibit lysosomal acidification and prevent fusion of autophagosomes with lysosomes. Studies have used autophagy inhibitors in combination with traditional chemotherapeutic agents that are known to induce autophagy in cancer cells, such as the mTOR inhibitor temsirolimus, or the alkylating agent temozolamide. More potent autophagy inhibitors are being developed and have shown promise in preclinical studies [80]. In addition to the lysosome, there are several other druggable therapeutic targets in the autophagy pathway, such as ULK1, VPS 34, ATG4, and ATG7, and numerous inhibitors are being developed against some of these targets [81]. It is likely that therapeutic regimens employing combinations of direct metabolic inhibitors and autophagy inhibitors will have synergistic effects in arresting the growth and survival of malignant cells.

Future directions

The precise regulatory systems involved in the interplay between cellular metabolism, autophagy, and nutrient flux in malignant cells are incompletely understood, but it is clear that these processes are intricately linked. Although recent metabolomic studies have reinforced the critical importance of autophagy induction in cancer cells under hypoxic conditions [82], further studies of this kind would be useful in elucidating important nutrient conditions that trigger autophagy and could determine the differential contributions of mTORC1-dependent and independent pathways to each of these processes. Precise metabolomic studies may also shed light on the specific fate of the products of

autophagolysosomal degradation, as well as track phospholipid membrane turnover as it relates to autophagic activity. In a similar regard, kinase activity assays may help to uncover the relative importance of various cell-signaling pathways in responding to a variety of metabolic conditions and, further, how these relate to induction or inhibition of autophagy. Development of systems that more closely approximate the *in vivo* tumor environment will allow better assessment of the contribution of cooperative metabolism to tumor growth and survival. Lastly, work in several groups has focused on microRNA as post-transcriptional control elements in autophagy, metabolism, and cancer. Studies have demonstrated that miRNA expression is significantly altered in stress and disease, with profound effects on the autophagic machinery [83].

As more detailed systems integrating metabolomics, kinase activity assays, and miRNA studies are developed, a more nuanced understanding of the role of autophagy, and its various subtypes, will likely emerge. Such studies should provide a more complete understanding of the seeming dual role of autophagy as both tumor promoter and suppressor, and uncover more specific targets for therapeutic control (Box 2).

Concluding remarks

Although the question as to whether malignancy should be considered primarily a state of disrupted cell signaling or one of perturbed cellular metabolism is an evolving area of discussion, it is clear that autophagic machinery is a prominent foot-soldier in supporting both signaling alterations and metabolic demands of the malignant phenotype. More study aimed at uncovering the mechanisms of integration between each of these processes will likely have profound implications for how cancer is understood, as well as offering a wellspring of promising therapeutic possibilities.

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Glossary

Aerobic glycolysis	an abnormally high rate of glucose conversion to lactate in the presence of oxygen tension typically sufficient to support oxidative phosphorylation. Known as the Warburg effect, aerobic glycolysis is a common metabolic process in cancer cells.
AKT	also known as protein kinase B (PKB), AKT is a serine–threonine kinase which plays an important role in growth factor signaling through the PI3K–AKT–mTOR pathway, as well as in cellular survival mechanisms, including regulation of apoptosis and autophagy.
Anaplerosis	the process of replenishing essential intermediates for maintenance of metabolic processes, particularly relevant to intermediates in the tricarboxylic acid (TCA) cycle.

Autophagy	a primary physiological pathway for intracellular degradation of cytosolic macromolecules and organelles by delivery via autophagosomes to lysosomes. Autophagy may be selective or non-selective and can operate at a basal rate, maintaining cellular homeostasis, or it may be upregulated during conditions of stress or starvation.
Autophagy-related genes (ATG)	a set of highly conserved genes (from yeast to mammals), that codes for proteins required for structural, regulatory, and functional performance of autophagic processes.
Cellular senescence	a quiescent state, wherein cells remain viable and active metabolically, but not capable of proliferation in response to mitogens.
Glutaminolysis	catabolic degradation of the amino acid glutamine to form glutamate, pyruvate, aspartate, lactate, citrate, and CO ₂ . Glutaminolysis allows cancer cells to use glutamine as a source of energy, supplying intermediates to the TCA cycle, and as a source of precursor molecules for macromolecule synthesis.
Hypoxia-inducible factors (HIFs)	a heterodimeric complex that senses and initiates response to varying cellular oxygen levels. Whereas Hif-1/2 α subunits are targeted for degradation in the presence of oxygen, they are stabilized and partner with Hif-1 β subunits in hypoxic conditions. This complex enters the nucleus and regulates gene expression important to survival in hypoxic conditions.
Mammalian target of rapamycin (mTOR)	a protein kinase and critical node in the PI3K/AKT/mTOR signaling pathway, at the nexus of cellular processes of growth and starvation. mTOR is the catalytic component of two distinct complexes, mTORC1 and mTORC2, which are differentiated by distinct accessory proteins. Taken as a whole, mTOR activity functions as a master nutrient-sensing complex, with central role in cellular growth regulation and homeostasis.
mTOR complex 1 (mTORC1)	a protein complex, responsive to cellular metabolic conditions, which regulates a vast array of cellular processes involved in growth and survival, including protein synthesis, metabolic flux, and autophagy.
mTOR complex 2 (mTORC2)	less well understood than mTORC1, mTORC2 regulates cytoskeletal changes as well as Akt signaling.
MYC	a transcription factor that activates a wide array of genes through binding to enhancer box sequences. MYC may also act as a gene repressor, as well as an agent of epigenetic remodeling via recruitment of histone acetyltransferases. Constitutively active in

	many cancers, MYC has wide-ranging effects on the transcriptome, especially in promoting cellular proliferation.
PI3K/AKT/ mTOR	a highly conserved growth factor-responsive signaling pathway and major regulator of cellular survival, metabolism, and cell growth. PI3K/AKT/mTOR is among the most commonly altered pathways in cancer.
RAS	a family of small GTPase proteins involved in cellular signal transduction, a subfamily of which (H-RAS, N-RAS, and K-RAS) are commonly mutated in human cancer. Ras proteins are integral members of the mitogen-activated protein kinase (MAPK) cascade, which promotes the expression of genes involved in growth and proliferation.

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Box 1. Autophagy as a tumor suppressor

Although upregulated autophagy acts as an accomplice for the metabolic changes associated with cancerous transformation, a well-regulated level of autophagy in normal cells may be associated with tumor suppression during the early stages of tumorigenesis. Initial evidence for this role came from the observation that mice with monoallelic deletion of the essential autophagy gene *BECN1* (Beclin1) are prone to hepatocellular carcinomas and other tumors [17,84]. Allelic loss of *BECN1* has also been identified in human tumors [85]. Although these results suggest that autophagy plays a major role in tumor suppression, this interpretation is confounded by the facts that Beclin1 has autophagy-independent cellular functions, and that tumor tissues and cells that have lost one allele of *BECN1* always retain one wild type (WT) copy, and in many cases are able to mount similar autophagic responses to stress as cells with two copies of *BECN1*. Tissue-specific deletion of *Atg5* – another essential autophagy gene that plays an important role in regulating apoptosis as well – has been shown to produce non-malignant hepatomas in mice. Defective autophagy in mice leads to accumulation of abnormal mitochondria, high levels of the adaptor protein P62, as well as increased DNA damage and genomic instability, each possibly contributing to accelerated tumorigenesis [13,86–88]. Furthermore, Ras-driven tumorigenesis may also be suppressed by autophagy-induced cellular senescence [50]. The role of autophagy in cancer, as either a tumor suppressor or promoter, is increasingly being understood as a context-dependent phenomenon, the specific triggers, inhibitors, and components of which are only starting to be understood.

Box 2. Outstanding questions

- What are the specific roles of the various subtypes of autophagy in both the prevention of cancer, on the one hand, and in the maintenance of tumorigenesis on the other?
- Will simultaneous inhibition of autophagy and cancer-specific metabolic processes act synergistically in therapeutic schemes?
- What are the specific destinies of the products of autophagic degradation, and what is the value of comprehensive metabolomic flux studies in this regard?
- What are the therapeutic implications of the identification of microRNA regulators on autophagy, and how are these networks altered in cancer cells?
- What is the significance and therapeutic implications of parasitic metabolic-autophagy models in tumor development and maintenance?

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Figure 1.

Stages of autophagy. Autophagy proceeds through stages of induction, vesicle nucleation, vesicle expansion, cargo recruitment, lysosomal fusion, and cargo recycling [10]. **(a)**

Induction is initiated by activation of the ULK1 complex. ULK1 complex activity is disinhibited by mTORC1- or AMPK-mediated phosphorylation. **(b)** Vesicle nucleation is the process whereby lipids and proteins are recruited for the initial steps in autophagosome formation. Lipid membrane may be derived from the mitochondria, endoplasmic reticulum (ER), plasma, or nuclear membrane. A phagophore assembly site (PAS) is initiated by phosphoinositide signals on source membrane that is generated through action of protein complexes that include VPS34 and BECLIN1. ULK1 complex is recruited to this site to initiate nucleation. **(c)** Vesicle expansion occurs as membranes expand at the PAS, eventually enclosing cytosolic cargo. This is accomplished through a cascade of ubiquitin-like conjugation systems involving an array of ATG proteins. **(d)** Recruitment of intracellular cargo (e.g., organelles and protein aggregates) to the developing autophagic vesicle is accomplished through adapter proteins, such as P62, neighbor of *BRCA1* gene (NBR1), and NIX. **(e)** Through a microtubule network, the formed autophagosome is transported to the lysosome with which it fuses to form an autophagolysosome. **(f)** Cargo is degraded by hydrolases within the acidic environment of the autophagolysosome.

Breakdown products are released into the cytosol via permeases. Abbreviations: ATG13, mammalian autophagy-related 13 homolog; ER, endoplasmic reticulum; PI3K, class III phosphoinositide 3-kinase; RB1CC1 (FIP200), RB1-inducible-coiled-coil 1; ULK1, Unc-51-like kinase 1; UVRAG, UV radiation resistance-associated gene protein; VPS34, vacuolar sorting protein 34.

Figure 2.

Autophagy supports cancer cell metabolism. Fueled by growth factor signaling and metabolic isozymes, oncogenic metabolism, including glutaminolysis, aerobic glycolysis, anapleurosis, and *de novo* lipid synthesis, cancer cell metabolism is in overdrive. Fueled by growth factor signaling and metabolic isozymes, oncogenic metabolism (i.e., glutaminolysis, aerobic glycolysis, anapleurosis, and *de novo* lipid synthesis) is a metabolism in overdrive. Autophagy, in turn, supports cancer cell metabolism by recycling aggregated proteins, damaged organelles, and cytosolic lipids, and by supplying amino acids, glucose, fatty acids, and acetyl-CoA for continued metabolism. Green lines represent pathways that regulate autophagy positively, either directly or indirectly through mTORC1-related pathways. Red lines represent pathways that inhibit autophagy. Abbreviations: AMPK, AMP kinase; HIFs, hypoxia inducible factors; LKB1 liver kinase B1; MAPK, mitogen-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; RHEB, Ras homolog enriched in brain; TSC1/2, tuberous sclerosis complexes 1/2.

Figure 3.

Cellular fates under normal and dysregulated conditions. Blue arrows denote cellular processes, their sizes indicating the relative magnitudes of different processes; black arrows denote the outcome of cellular conditions. **(a)** Under normal physiologic conditions cellular homeostasis is maintained by balancing growth signaling, cellular metabolism, and recycling of organelles and cellular macromolecules by basal autophagy. **(b)** Under conditions of Ras-mutated growth signaling, cellular stress signals are activated, and progression to a fully oncogenic phenotype is avoided by P53 or by autophagy-mediated senescence or cell death. **(c)** In a fully oncogenic phenotype, autophagy upregulation, fueled by oncogenic signaling, nutrient deficits, hypoxia, and stress signals, acts to support dysregulated metabolism, becoming an ally in enabling a hyperproliferative, hypermetabolic state. Abbreviations: ER, endoplasmic reticulum; ROS, reactive oxygen species.