MINI REVIEW

Targeting Mitochondrial Metabolism by Inhibiting Autophagy in BRAF-Driven Cancers

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ABSTRACT

Metabolomic analyses of human tumors and mouse models of cancer have identified key roles for autophagy in supporting mitochondrial metabolism and homeostasis. In this review, we highlight data suggesting that autophagy inhibition may be particularly effective in BRAF-driven malignancies. Catalytic BRAF inhibitors have profound efficacy in tumors carrying activating mutations in Braf but are limited by the rapid emergence of resistance due in part to increased mitochondrial biogenesis and heightened rates of oxidative phosphorylation. We suggest that combined inhibition of autophagy and BRAF may overcome this limitation.

Significance: BrafV600E-driven tumors require autophagy and likely autophagy-provided substrates to maintain mitochondrial metabolism and to promote tumor growth, suggesting that autophagy ablation may improve cancer therapy. Cancer Discov; 4(7): 766-72. ©2014 AACR.

INTRODUCTION

The altered metabolic profile of cancer cells has been known for decades, but the optimal means to exploit these differences therapeutically has remained elusive. At a fundamental level, an actively proliferating cancer cell must meet three basic needs: preservation of ATP generation, continued access to a supply of substrates for macromolecular synthesis, and management of oxidative stress (1). Macrouathagy (hereafter autophagy) is intimately related to all these processes, explaining its role in promoting tumor growth and chemotolerance of numerous therapeutic modalities, and interest in the development and application of autophagy-inhibiting strategies for cancer.

Autophagy is a highly conserved catabolic process that sustains metabolism during times of nutrient insufficiency by capturing, degrading, and recycling damaged or superfluous intracellular components into metabolic pathways. Basal autophagy is constitutively active at low levels in most tissues and maintains protein and organelle quality by the selective elimination of damaged intracellular material. The autophagy pathway is dramatically upregulated in response to stress and starvation, where it plays a critical role in removing damaged organelles and aggregated proteins whose accumulation is toxic. Stress-stimulated autophagy also ensures the continued supply of substrates (nucleosides, amino acid, lipids, and carbohydrates) to the cell to support metabolism in the absence of exogenous nutrients (2).

Autophagy is executed by the concerted action of the multiple autophagy-related ATG gene products, first identified in yeast. The mechanics of autophagosome nucleation and expansion are complex, and we refer the readers to several excellent reviews on this subject (3, 4). Briefly, damaged or misfolded proteins and organelles are ubiquitinated, recognized by the autophagy cargo receptors, and delivered to autophagosomes, which subsequently fuse with lysosomes wherein cargo is degraded by acid hydrolases and recycled back to the cytoplasm for repurposing. Other more selective types of autophagy exist that target specific organelles, such as mitochondria (mitophagy) and peroxisomes (peroxophagy), as well as the more recently described microautophagy (5, 6).

Mosaic, constitutive, and tissue-specific deletion of autophagy in mice has firmly established the role of the pathway in supporting metabolism. Autophagy is essential for survival during perinatal starvation (7, 8) and preimplantation tissue remodeling (9), and prevents liver damage, muscle wasting (10), and neurodegeneration (11, 12).

Autophagy may play a dual role in cancer. In some contexts, autophagy suppresses tumor initiation by preventing chronic inflammation and genetic instability. However, in other situations, such as in established tumors, autophagy seems to promote tumor cell survival by maintaining metabolism via catabolism of cellular components and by preventing the toxic build-up of dysfunctional proteins and organelles (13–16). Achieving a more complete understanding of the contextual role of autophagy in cancer and identifying patient populations that would maximally benefit from autophagy-inhibiting therapies are unmet challenges for the
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KEY CONCEPTS

- Autophagy is a survival mechanism exploited by tumor cells to meet their elevated metabolic demands and to tolerate stress.
- Autophagy sustains mitochondrial metabolism and promotes tumor growth by degrading intracellular components to replenish tricarboxylic acid (TCA) cycle substrates that support homeostasis and macromolecular synthesis.
- Oncogenic BRAF creates a dependency on oxidative phosphorylation required for tumor establishment and maintenance by modulating pyruvate entry into the TCA cycle.
- Sustained inhibition of BRAF results in increased mitochondrial biogenesis and enhanced stress tolerance in melanoma, undermining treatment efficacy.
- Autophagy ablation in models of BrofV600E-driven cancer impairs mitochondrial metabolism and increases the survival of BrofV600E tumor-bearing mice.
- BrofV600E-driven malignancies may be particularly susceptible to autophagy-inhibiting strategies.

research community. Genetically engineered mouse models of cancer with autophagy defects and metabolomic analyses of human and murine tumors are providing important insights into these areas.

MITOCHONDRIA PLAY KEY ROLES IN CANCER

Otto Warburg’s (17) observation that tumor cells preferentially engage glycolytic rather than oxidative metabolism in nutrient-replete conditions (i.e., the Warburg Effect) led to speculation that defects in mitochondrial function occur in and may contribute to tumorigenesis. Although the Warburg Effect predicted the existence of wholly nonfunctional mitochondria, this has been shown not to be the case, leading to the suggestion that cancer-associated metabolic reprogramming may be the result of the oncogenic events themselves (18). Critically, even in tumor cells with high glycolytic flux, such as those transformed by oncogenic AKT or RAS, mitochondria are functional, with glutamine-supported oxidative phosphorylation constituting a major source of cellular ATP under both normoxic and hypoxic conditions (19). Above and beyond their role in ATP production, mitochondria generate citrate (critical for acetyl-CoA generation for fatty acid synthesis and chromatin modification), give rise to NADPH equivalents (needed for lipogenesis, de novo synthesis, and redox homeostasis), support the production of amino acids, and generate iron–sulfur clusters (required for electron transport; refs. 20, 21). Mitochondria also sequester potent apoptosis-inducing proteins from the cytosol such as cytochrome c. Thus, mitochondria are critical for numerous cellular functions, and regulating their spectrum of activity and fitness is essential for most, if not all, cells. Autophagy supports mitochondrial function by providing substrates for the tricarboxylic acid (TCA) cycle and by eliminating damaged mitochondria in a process called mitophagy. Recall that mitophagy is the sole mechanism by which cells can eliminate damaged mitochondria, the failure of which broadly affects cellular and organismal function. This may explain why autophagy defects are predominantly detrimental.

The functional importance of mitochondria in tumorigenesis was first suggested by studies with rho-zero (ρ°) cells in which mitochondrial DNA was eliminated by a long-term culture in ethidium bromide. These cells display proliferative defects, reduced colony formation, and impaired tumor growth in nude mice (22–24). Critically, genetic deletion of mitochondrial transcription factor A (TFAM), which disables mitochondrial function, abrogated tumorigenesis in a KrasG12D-driven model of lung cancer (25). Similarly, loss of mitochondrial p32 led to compromised oxidative phosphorylation and diminished tumorigenesis (26). Thus, although the cell is capable of generating energy and reducing equivalents from other pathways, retaining a functional mitochondrial pool (i.e., oxidative phosphorylation competent) is critical for tumorigenesis, likely in part for the reasons enumerated above. Taken together, these data suggest that acutely targeting mitochondrial metabolism may be a successful and novel therapeutic strategy for cancer. Autophagy inhibition may be one way to do this.

AUTOPHAGY IS A SURVIVAL FACTOR EXPLOITED BY TUMOR CELLS

As with normal cells, tumor cells can access the survival-promoting functions of autophagy to facilitate tumorigenesis, and determining the circumstances and the underlying mechanisms by which they do so is likely to provide new approaches to cancer therapy. Autophagy localizes to hypoxic regions of tumors, where it enables tumor cell survival (27). Human tumors commonly possess elevated rates of basal autophagy, which are correlated with poor outcome and increased tumor survival (28–30). This increased autophagic activity serves crucial roles for the cancer cell: mitigation of oxidative stress, thereby preventing activation of a senescence checkpoint that could limit tumorigenesis, and ensuring a continued supply of substrates for mitochondrial metabolism that supports the elevated metabolic and biosynthetic demands of a rapidly proliferating cancer cell.

Work from multiple groups has established that autophagy is particularly needed by cells to cope with oncogenic stress (31). Expression of oncogenic RAS in isogenic Atg5+/− or Atg5−/− immortalized baby mouse kidney (iBMK) cell lines upregulates basal autophagy even in nutrient-replete conditions. RAS-expressing autophagy-defective cells are more sensitive to starvation in Hank’s Balanced Salt Solution (HBSS) than their autophagy-competent counterparts and are impaired in their ability to form tumors in nude mice, leading to their designation as “autophagy addicted” (30). In agreement with these data, pancreatic and immortalized mammary epithelial cell lines harboring oncogenic RAS mutations are similarly dependent on autophagy for continued proliferation and anchorage-independent growth (32, 33). In addition, recent work has linked autophagy-dependent secretion to invasion in RAS-transformed cells (34). The tumor-promoting
function of autophagy has been further confirmed in genetically engineered mouse models of cancer. Deletion of Atg7 in BrafV600E- or KrasG12D-driven models of lung cancer alters tumor cell fate to oncocytes, poorly understood benign lesions characterized by an accumulation of defective mitochondria, and increases survival independent of Trp53 status (35–38). Likewise, ablation of Atg5 in a KrasG12D-driven model of lung cancer is associated with profound mitochondrial defects and increased survival (39), and deficiency of Bedim1/Atg6 or Fip200/Atg17 delays mammary tumorogenesis (40, 41). Similarly, deficiency of Atg5 in a KrasG12D-driven pancreatic cancer mouse model extends lifespan when Trp53 is wild-type, suggesting that the tumor-promoting role of autophagy in some settings is mediated by the suppression of p53 (42). Indeed, less autophagy dependence is seen in other cancer models when p53 is also inactivated (31). These data suggest that inhibiting autophagy is likely to be a powerful approach for a variety of tumor types. Determining the exact mechanism by which autophagy promotes cancer in these different contexts is therefore of the utmost importance.

**AUTOPHAGY SUSTAINS MITOCHONDRIAL METABOLISM**

Autophagy-deficient tumors and tumor-derived cell lines (TDCL) from BrafV600E- or KrasG12D-driven mouse models of lung cancer accumulate ultrastructurally abnormal mitochondria, possess a smaller pool size of healthy mitochondria, are exquisitely sensitive to starvation, and are impaired in their ability to form tumors in nude mice, recapitulating the phenotype of autophagy addiction in mouse models of cancer. Autophagy-deficient BrafV600E TDCLs have a defect in mitochondrial respiration, evidenced by significantly reduced oxygen consumption rates (OCR) under normal growth conditions and starvation. Importantly, the reduced OCR and sensitivity to starvation of the autophagy-null cell lines can be rescued by the addition of exogenous glutamine, demonstrating that nutrient limitation is responsible for the compromised survival in HBSS. This key result establishes that autophagy sustains mitochondrial metabolism by providing amino acids, such as glutamine from protein degradation (and perhaps other components), that are essential for cancer cell survival. It remains to be seen whether the phenomenon of autophagy addiction is essentially an addiction to glutamine, apparent in many other cancers during adaptation to the transformed state, or whether there are additional autophagy-supplied materials that are essential for viability. Taken together, it seems that tumors are addicted to autophagy to maintain a functional mitochondrial pool and to ensure the continuous replenishment of the TCA cycle components, a process known as anapleurosis, critical for the maintenance of cellular homeostasis. These data are consistent with the work of Suzuki and colleagues (43), who demonstrated that autophagy is required to prevent mitochondrial impairment in yeast. Autophagy-inhibiting strategies for cancer are thus predicted to compromise mitochondrial metabolism, making this approach broadly applicable for cancer. Although the present work used material derived from Atg7−/− tumors, multiple studies have demonstrated that the small-molecule inhibitor of autophagy chloroquine is capable of significantly impairing mitochondrial respiration, indicating that even an incomplete autophagy blockade is sufficient to alter mitochondrial metabolism (33, 44, 45).

The rescue of the survival of autophagy-deficient TDCLs by glutamine is satisfying as it fits well with our present understanding of autophagy as a means to support metabolism during nutrient scarcity. Glutamine is the most abundant amino acid in the serum and a key anaplerotic source for the cell, particularly important in hypoxic and glucose-limiting contexts (46). Through glutaminolysis, glutamine is converted to α-ketoglutarate in a two-step process: first modified to glutamate via glutaminase releasing ammonia as a byproduct, and then converted to α-ketoglutarate by glutamate dehydrogenase. The release of ammonia is important, as it has recently been shown to be an autophagy inducer in its own right (47). Glutamine can also generate pyruvate and NADPH equivalents en route to conversion to lactate by the activity of malic enzyme. A second, indirect mechanism to generate acetyl-CoA from glutamine exists in which glutamine is converted to glutamate, then to α-ketoglutarate, and then to citrate. Citrate makes acetyl-CoA via IDH1 (46, 48). Glutamine donates nitrogen for purine and pyrimidine biosynthesis, and supports amino acid biosynthesis (reviewed in ref. 49). Many tumors are dependent on glutaminolysis for survival, leading to investigations of glutaminase inhibitors for cancer therapy. Autophagy-inhibiting strategies may have a more favorable toxicity profile than glutaminase inhibitors, as they would limit only autophagy-supplied glutamine entry into the TCA cycle, while sparing glutamine catabolism itself.

It is known that that both the tissue type and the individual oncogenic insults contribute to the metabolic profile of a tumor (50), suggesting that there is not likely to be a universal inhibitor of cancer metabolism. Thus, it will be of great importance to understand how autophagy supports the metabolism of specific tumor types, and if and how specific driver mutations affect this program. Tracer studies, in which the cell is fed isotope-labeled substrate (typically glucose or glutamine) and analyzed by LC/MS, will inform these investigations. These approaches are particularly powerful when combined with genetically defined cancers from engineered mouse models of cancer, or even better still, the mice themselves.

**ONCOGENIC BRAF INDUCES DEPENDENCE ON OXIDATIVE PHOSPHORYLATION**

BRAF mutations are found in melanoma (65%) and hairy cell leukemia (100%), as well as in tumors of the lung (3%), colon (18%), papillary thyroid (40%), and ovary (4%), and in a subset of low-grade pediatric gliomas called pleomorphic xanthoastrocytomas (60%; refs. 51–55). The most common mutation is a V600E mutation in the kinase domain, resulting in constitutive activity and sustained ERK signaling. BRAFV600E drives oxidative phosphorylation at the expense of glycolysis by controlling pyruvate metabolism. Kaplan and colleagues (56) demonstrated that the coordinate decrease in pyruvate dehydrogenase (PDH) complex kinase 1 (PDK1) activity and increase in PDH phosphatase 2 (PDP2) activity result in robust activation of the PDH complex, and
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**Figure 1.** Inhibiting autophagy in BRAFV600E-driven cancers. In BRAFV600E-driven mouse models of lung cancer, autophagy mitigates ROS production and provides glutamine to fuel the TCA cycle. In parallel, BRAFV600E drives entry of pyruvate into the TCA cycle by coordinate regulation of PDK1 and PDP2, leading to increased oxidative phosphorylation. This dual driving of the TCA cycle results in adenoma (in p53-intact tumors) or adenocarcinoma (in p53-deficient tumor’s) formation, illustrated here by the purple tumor cells. Arrow weight indicates flux through the TCA cycle. Autophagy ablation alters tumor cell fate to oncocytoma, a benign tumor type characterized by an accumulation of defective mitochondria in their cytoplasmic compartments (represented here by the enlarged pink tumor cells). These tumors possess proliferative defects, and perhaps in other model systems this increased flux through the TCA cycle may result in senescence. Autophagy deficiency impairs the TCA cycle flux. The defects in respiration associated with autophagy deficiency may be the consequence of both substrate reduction and/or accumulation of defective mitochondria (due to failure to eliminate these organelles through mitophagy). Combined blockade of autophagy and BRAF is predicted to be synthetically lethal. Refer to text for more details.

that this rewiring leads to enhanced oxidation of pyruvate in the TCA cycle (Fig. 1). Adenoviral delivery of PDK1 to p53-depleted melanocytes derived from TyrCreER; BrafV600E-mutant mice leads to significant tumor growth in xenografts, indicating that PDK1 levels can override senescent signaling to drive tumorigenesis. Conversely, knockdown of PDK1 impairs tumor formation in nude mice and leads to regression of established tumors. Importantly, the combination of PDK1 silencing and PLX4720 (a preclinical analogue of the BRAFV600E inhibitor vemurafenib) was sufficient to sensitize even strongly resistant melanoma cell lines (56). More recently, deletion of PDK1 or its pharmacologic inhibition was shown to delay tumorigenesis in a mouse model of metastatic melanoma (57). This provides evidence that metabolic modulation influences the oncogenic function of BRAFV600E and may augment targeted therapy.

Similarly, sustained treatment of melanoma cells with BRAF inhibitors induces addiction to oxidative phosphorylation by altering mitochondrial pool sizes (58, 59). BRAFV600E normally suppresses expression of PPAR-γ coactivator 1α (hereafter PGC1α). BRAF inhibitors relieve this repression, enabling increased PGC1α-driven mitochondrial biogenesis, enhanced oxidative phosphorylation (due to increased mitochondrial pool size), and a corresponding increase in stress tolerance and tumor survival that undermines therapeutic efficacy. The effect is lineage-specific, controlled by expression of the melanocyte-specific transcription factor microphthalmia-associated transcription factor (MITF). Of note, amplification of MITF is one of the commonly detected mechanisms of resistance to the catalytic BRAF inhibitors (60). These data suggest that strategies targeting mitochondrial function are likely to be synthetically lethal when delivered in combination with BRAF inhibitors. The efficacy of this approach was illustrated by the recent work of Yuan and colleagues (61), reporting that the combination of the biguanide and mitochondrial complex I inhibitor phenformin with the BRAF inhibitor vemurafenib induces tumor regression in xenografts and in a genetically engineered model of BrafV600E+/-; Pten-/--driven melanoma. BRAFV600E-mutant tumors are impaired in their ability to activate S’ AMP-activated protein kinase (AMPK) due to ERK-mediated phosphorylation and inactivation of LKB1. Thus, BRAFV600E-mutant tumors may be particularly vulnerable to metabolic insults due to an inability to respond normally to energy crisis (62, 63). Phenformin and metformin are AMPK-activating agents in addition to inhibiting complex I; both functions may be at the root of the synergy with BRAF inhibition.

**COMBINED AUTOPHAGY AND BRAF INHIBITION AS AN IMPROVED THERAPEUTIC REGIMEN FOR CANCER**

The catalytic BRAF inhibitors vemurafenib and dabrafenib induce dramatic yet relatively short periods of antitumor activity before the emergence of resistance and treatment failure. Thus, there is a considerable interest in the identification of combination therapies that could delay resistance. Notable side effects of the BRAF inhibitors include the appearance of benign skin tumors and occasionally squamous
cell carcinomas. Also of concern is an acceleration of pre-existing RAS-mutant growths in the colon and appearance of RAS-driven leukemias, which are thought to arise due to ERK activation in the adjacent wild-type BRAF tissue (reviewed in ref. 60; see also ref. 64). RAS activation causes dimerization and activation of wild-type BRAF. BRAFV600E signals as a monomer. This difference is of central importance, as inhibitors binding to a single component of the dimer in wild-type BRAF triggers allosteric activation of the remaining protein, resulting in ERK activation. Combined RAF and MEK inhibition is thought to reduce the risk of appearance of these tumors, although it does not completely eradicate them, and is being assessed in active clinical trials. RAS- and BRAF-driven tumors are exquisitely sensitive to autophagy inhibition (32, 33, 37, 38). We suggest that the combined blockade of autophagy and oncogenic BRAF may be particularly efficacious as BRAF-driven tumors induce and require mitochondrial metabolism, and therefore may need autophagy to supply substrates, such as glutamine, to replenish TCA cycle intermediates and to eliminate damaged mitochondria.

Autophagy ablation is known to reduce the pool size of functional mitochondria and significantly impair mitochondrial respiration, which may be especially deleterious to tumor cells already heavily reliant on oxidative phosphorylation for survival, such as those driven by oncogenic Braf. Autophagy-inhibiting therapies may be preferable to treatment with the biguanides or PDK1 inhibition despite the prediction that all three approaches target oxidative phosphorylation, as treatment with Braf inhibitors upregulates autophagy in cell lines and tumors, and autophagy more broadly affects mitochondrial metabolism. Importantly, this enhanced autophagy was correlated with reduced progression-free survival in BRAFV600E inhibitor–resistant melanomas both at baseline and at time of progression (65). It may be that as the catalytic BRAF inhibitors relieve the PGC1α repression and increase mitochondrial biomass but blunt entry into the TCA cycle, the contribution of autophagy-supplied glutamine becomes critical for survival, rendering these tumors exquisitely sensitive to autophagy-blocking therapies. Intriguingly, recent work by Ma and colleagues demonstrated that the autophagy inhibitor Lys05 was sufficient to induce tumor regression in xenograft models of BRAF inhibitor–resistant melanoma, providing further support for this model (65, 66).

As with all targeted therapies, autophagy-inhibiting strategies will be most effective in situations in which the pathway is heavily relied upon, as in the case of highly metabolically active tumor cells. A synthetic lethal approach to eliminate treatment-induced senescent (TIS) cells in the Eµ-Myc model of lymphomas based on this principle was recently described (67). Despite the lack of a definitive role for autophagy in senescence, it seems that autophagy facilitates senescence or at least is required to support the senescence-associated secretory phenotype (SASP) and its production of inflammatory cytokines and elevated rates of protein synthesis (68). Indeed, mTOR and mature autophagosomes colocalize in a compartment called the mTOR autophagy spatial coupling compartment (TASCC) while secreting IL6 and IL8, key components of the SASP, supporting this theory (69). The approach of Dorr and colleagues (67) is based on the “hypermetabolic state” of TIS cells as they mount the SASP response following acute treatment with cyclophosphamide; features include increased glucose utilization, increased ATP production, enhanced fatty-acid and oxygen consumption, and increased stress due to SASP. TIS-competent cells that displayed this hypermetabolic state are remarkably sensitive to autophagy inhibition or to other agents that limit metabolic capacity. Combination therapy of cyclophosphamide and the autophagy inhibitor bafloymycin A1 extended survival in TIS-competent mice. Critically, the authors demonstrate that the hypermetabolic state is detectable in primary blast cells from patients with acute myelogenous leukemia and correlates with sensitivity to autophagy-blocking agents. The next important step will be the development of assays that can rapidly identify SASP in patients, thereby identifying populations that would benefit from autophagy-blocking therapies.

These strategies all take advantage of the fact that the targeted cell is metabolically stressed and barely manages to get by with the assistance of productive autophagy. Autophagy ablation “puts the cell over the edge,” leading to fatal consequences, which we predict will contribute to more favorable outcomes in the clinic for patients.

CONCLUDING REMARKS

Autophagy is upregulated to meet the increased metabolic demands of actively growing tumors and constitutes a resistance mechanism to many therapeutic modalities. Tumors rely on autophagy to eliminate damaged mitochondria and to supply substrates for oxidative metabolism. Thus, autophagy inhibition is a novel and potent means to target mitochondrial metabolism in cancer with broad applicability to human tumors. Here we have discussed the potential utility of autophagy-blocking strategies in BRAF-driven malignancies due to their reliance on oxidative phosphorylation, which may be the basis for oncogene addiction to autophagy. The potential therapeutic efficacy of autophagy inhibition in cancer has generated intense interest within the research community and led to the development and execution of numerous clinical trials investigating the consequences of autophagy inhibition with the FDA-approved small-molecule autophagy inhibitors chloroquine and hydroxychloroquine (www.clinicaltrials.gov). The complexity of human tumors and their ability to adapt to evolving conditions suggests that combination therapies incorporating autophagy inhibition would be preferable to single-agent regimens. Although the vast majority of these clinical trials are ongoing, the results of several recent studies suggest that hydroxychloroquine can be safely added to a variety of therapeutic regimens at doses that inhibit autophagy without undue toxicity, and suggest that this intervention may have clinical benefit in a variety of tumor types (70–73). Although data from ongoing clinical trials are encouraging, there are cautionary notes before autophagy-modulating agents can be deployed as a therapeutic strategy for cancer. First, as we have shown that autophagy suppresses early tumorigenesis of Braf-driven lung cancer by mitigating oxidative stress (38), potential settings in which autophagy inhibition may be counterproductive need to be considered. Acute autophagy ablation may be preferable, as the deleterious effects of long-term
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Autophagy ablation, including accumulation of damaged, ROS-producing mitochondria and SQSTM1/p62 due to failed protein and organelle quality control that can contribute to genetic instability and tumorigenesis, have been well established (13, 14, 27, 38, 74). Moreover, there is an unmet need for the development of more specific autophagy inhibitors for use in the clinic. At present, most studies use chloroquine or hydroxychloroquine, which block lysosomal functions and may have unrelated effects. Finally, a clear approach to delineate the degree of selectiveness of autophagy inactivation in tumor versus normal tissue and identification of a panel of biomarkers that can be used to monitor the efficacy of autophagy-inhibiting therapies (in addition to LC3, p62 levels, and autophagosome formation by electron microscopy) are needed. Further mechanistic studies will shed light on the most optimal patient subpopulation, drug combinations, and new targets for anticancer drug discovery.

Disclosure of Potential Conflicts of Interest

E. White is a consultant/advisory board member of Forma Therapeutics. No potential conflicts of interest were disclosed by the other authors.

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