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Fabio Ferro[1], Stéphane Servais[1], Pierre Besson[1], Sébastien Roger[2], Jean-François Dumas[1] & Lucie Brisson[1]

[1] Université de Tours, Inserm, UMR1069 Nutrition, Croissance et Cancer, Tours, France

[2] Université de Tours, EA4245 Transplantation, Immunologie et Inflammation, Tours, France

Corresponding author lucie.brisson@univ-tours.fr,

UMR Inserm 1069, Université de Tours, 10 Boulevard Tonnellé, 37032 Tours,

Abstract

Metabolic reprogramming in tumours is now recognized as a hallmark of cancer, participating both in tumour growth and cancer progression. Cancer cells develop global metabolic adaptations allowing them to survive in the low oxygen and nutrient tumour microenvironment. Among these metabolic adaptations, cancer cells use glycolysis but also mitochondrial oxidations to produce ATP and building blocks needed for their high proliferation rate. Another particular adaptation of cancer cell metabolism is the use of autophagy and specific forms of autophagy like mitophagy to recycle intracellular components in condition of metabolic stress or during anticancer treatments. The plasticity of cancer cell metabolism is a major limitation of anticancer treatments and could participate to therapy resistances. The aim of this review is to report recent advances in the understanding of the relationship between tumour metabolism and autophagy/mitophagy in order to propose new therapeutic strategies.

Keywords:

Cancer metabolism, autophagy, mitophagy, ROS, mitochondria, ion channel

Abbreviations:

- AMPK: AMP-activated protein kinase
- CAF: cancer associated fibroblast
- Drp1:dynamin-related protein 1
- EMT: epithelial-to-mesenchymal transition
- ER: endoplasmic reticulum
- FA: fatty acid
- FAO: fatty acid oxidation
- HIF: Hypoxia-inducible factor
- IMM: inner mitochondrial membrane
- IMS: intermembrane space
- IP3R: Inositol trisphosphate receptor calcium channel
- MAM: mitochondrial-associated ER membrane
- MCU: mitochondrial calcium uniporter
- OMM: outer mitochondrial membrane
- OXPHOS: oxidative phosphorylation
- PE: phosphatidylethanolamine
- PS: phosphatidylserine
- ROS: reactive oxygen species
- TCA: tricarboxylic acid
- TRP: transient receptor potential channel
- VDAC: voltage-dependent anion channel

Introduction

In solid tumours, cancer cells are subjected to very strong and selective metabolic pressures because of limited oxygen and nutrient availability. It is now recognised that the tumour microenvironment has a critical effect on cancer cell selection, tumour growth and progression. Only the most metabolically adapted cancer cells will survive to this inhospitable microenvironment, and to the stress factors generated by anticancer treatments. Notably, the metabolic plasticity of cancer cells allows them to use various metabolic substrates. Furthermore, the recycling of intracellular components through autophagy participates to the production of metabolic precursors to sustain cell growth. These adaptations are critical for tumour growth, metastasis appearance and the acquisition of resistances to anticancer treatments. One major challenge for the development of new anticancer treatments is to limit the metabolic adaptations of cancer cells which could allow better therapeutic efficacy and avoid the acquisition of resistance mechanisms. Because mitochondria and autophagy participate to the metabolic adaptation of cancer cells, one potential strategy would be to target related pathways in order to limit the acquisition of resistance to anticancer treatments. This review summarizes recent advances in the understanding of the regulation of autophagy by mitochondria through the control of energy metabolism, reactive oxygen species production and mitochondrial-associated ER membranes. Reciprocally, the regulation of mitochondrial mass and functioning by mitophagy will be discussed. We will focus on mitochondrial calcium transporters as potential new therapeutic targets for autophagy/mitophagy in cancer treatment.

1. Targeting mitochondrial metabolism and autophagy in cancer

1.1. Mitochondrial metabolism in tumours

Mitochondria are major organelles with primary roles in energy production, Ca^{2+} and redox homeostasis, and apoptosis. It has long been thought that cancer cells do not produce energy by mitochondrial oxidation but through a high glycolytic rate coupled with lactic acid production even in presence of oxygen namely the Warburg effect (or aerobic glycolysis) [1]. Despite the initial characterization of a major role of aerobic glycolysis in cancer cells, it is now recognized that mitochondrial oxidative phosphorylation (OXPHOS) is not impaired in all cells constituting tumours and participates to ATP production [2]. In fact cancer cell metabolism is more complex than initially described related to oxygen availability, with the use of a wide range of substrates including glutamine [3], lactate [4] or fatty acids [5] to fulfil metabolic demands. The global reprogramming of cancer cell metabolism not only supports the production of ATP in metabolic stress conditions but also leads to the production of building blocks (amino acids, fatty acids, nucleotides) needed for a

high proliferation rate [6]. These building blocks are produced by the tricarboxylic acid (TCA) cycle uncoupled to ATP production by OXPHOS (cataplerosis) providing oxaloacetate and α-ketoglutarate for the synthesis of amino acids and citrate as a shuttle for the export of acetyl-coA to the cytosol for lipid synthesis. Furthermore an important part of the biomass is derived from glutamine and other amino acids which are able to replenish TCA cycle intermediates (anaplerosis) for amino acid biosynthesis [7]. Metabolites from glycolysis and the pentose phosphate pathway are additional important precursors for the synthesis of nucleotides and amino acids needed for cancer cell proliferation [6].

Through its important contribution in the production of ATP and macromolecules, it is now well described that mitochondria sustain tumour growth and cancer progression. Indeed mitochondrial function has been associated with cancer cell proliferation, resistance to cell death and metastasis (see reviews [8-11]). Consequently, targeting mitochondria in cancer cells has been proposed to reduce tumour progression [12-14].

1.2. Autophagy

Autophagy is a cellular catabolic pathway leading to the degradation and recycling of proteins and organelles, following the fusion between an isolation vesicle, the autophagosome, and a lysosome providing hydrolytic enzymes. Macroautophagy (hereafter called autophagy) is a non-selective form of autophagy, whereas several forms of autophagy are selective for intracellular organelles like mitochondria and therefore called mitophagy (see section mitophagy). The molecular process of autophagy is complex and involves sequential steps of nucleation, elongation, and fusion through several proteins including the autophagy-related (Atg) proteins (for review [15-17]). Autophagy connects substrate availability in the environment with cellular metabolic requirements. Indeed, autophagy is activated by nutrient starvation, as well as under oxidative stress conditions, through highly regulated pathways linked with energy metabolism. These pathways mostly converge on mTORC1 and the energy-sensing AMP-activated protein kinase (AMPK) [18-21]. Autophagy has two major physiological roles: the breakdown of dysfunctional proteins or organelles as a quality control mechanism, and the recycling of macromolecules under nutrient stress conditions in order to sustain metabolic demands [22, 23].

It is now well admitted that autophagy can have two roles in cancer: protective at early stage of the tumour but promoting tumour growth at later stages [24, 25]. Knockout of autophagy genes in mice increases tumour multiplicity mainly by increasing oxidative stress, indicating that autophagy protects against cancer development [26, 27]. However, in established tumours, the activation of

autophagy by the extracellular conditions (hypoxia, low nutrients and growth factors, reactive oxygen species (ROS), and lactate) [28-30] and by oncogenes Ras and p53 [31] sustains the survival of cancer cells and is favourable to tumour growth [24, 28, 32, 33]. In addition, autophagy plays a prominent role in the tumour microenvironment by modulating the interactions between cancer cells and non-cancer cells from the tumour [34, 35]. Besides these apparently opposite roles in tumour initiation and tumour growth, autophagy has also been associated with cancer progression. Markers of autophagy are increased in metastases compared with primary tumours [36] and are associated with poor prognosis [37, 38]. The role of autophagy in metastasis formation is complex but it is now proposed that autophagy participates to all the different steps of the metastatic cascade. Indeed, recent evidence suggest that autophagy promotes cancer cell migration, invasiveness, epithelial-to-mesenchymal transition (EMT) and anoikis resistance [39]. Autophagy regulates focal adhesion disassembly through direct degradation of paxillin and thus promotes cancer cell migration and metastasis [40]. Interestingly, the autophagic process can promote the secretion of the pro-migratory cytokine interleukin-6 (IL-6), matrix metalloproteinase 2 and WNT5A participating both in cancer cell migration and extracellular matrix degradation [41]. This unconventional function of autophagy has been described to promote cancer progression through secretion of proteins stimulating invasiveness, angiogenesis and limiting immunosurveillance [42]. Furthermore, autophagy is activated during matrix detachment and promotes anoikis resistance, thus allowing cancer cell survival in vessels and during metastatic colonization [43, 44]. Although the molecular mechanism is not clearly understood and depends on cancer models and status, autophagy has been associated with EMT, a process that participates to both cancer metastasis and resistance to anticancer treatments [45]. Autophagy is also activated during anticancer treatments by radiation therapy and chemotherapy. Whether autophagy is associated with cell death during cancer treatment or with cell survival and resistance to anticancer treatments is still debated. However it is now demonstrated in different models that inhibition of autophagy can sensitize cancer cells to several anticancer treatments [46-52].

To date, hydroxychloroquine (HCQ), a weak base, lysosomotropic agent, used as an anti-malarial drug, is the only autophagy inhibitor clinically available. HCQ has been tested in several clinical trials as a broad spectrum inhibitor of autophagy in association with chemotherapy or radiotherapy. In patients with several types of solid tumours, studies showed the safety of HCQ and its ability to target autophagy [53]. However, its use is limited by side effects independent of autophagy [54-56]. Furthermore, HCQ activity decreases with acidity, which is found in the extracellular compartment around tumours [57]. Therefore, a better understanding of the regulations of autophagy is needed to propose new strategies for targeting cancer, depending on tumour type, stage and metabolism.

1.3. Mitochondrial metabolism in regulation of autophagy

1.3.1. Energy metabolism

Besides the activation of autophagy by low nutrient availability in the tumour microenvironment, the metabolic reprogramming of tumour cells can also support autophagy activation (Figure 1). Autophagy is highly regulated by ATP production and AMPK pathway. Therefore, a reduction of ATP production leads to the accumulation of AMP, the activation of AMPK and autophagy. Indeed, mitochondrial dysfunction induced by the inhibition of respiratory chain and complex III knock-out activates AMPK and autophagy [58, 59] to promote cell survival [59]. Autophagy is transcriptionally regulated during starvation by the induction of transcription factor TFEB which activates the transcription of Atg genes [60]. The acute inhibition of mitochondrial OXPHOS induces the expression of TFEB and lysosomal biogenesis [61], which can also participate to the activation of autophagy by mitochondrial dysfunction in cancer.

Unlike the activation of autophagy by mitochondrial dysfunction, it has been demonstrated in yeast and in mammalian cells that mitochondrial activity is required for autophagy induction [62, 63]. In yeast, amino acid starvation required functional mitochondria to induce LC3 expression and the activation of autophagic flux [62]. Interestingly, it has been demonstrated that mitochondria regulates autophagy through the cAMP-dependent kinase PKA [62]. It is not known whether this requirement of mitochondrial activity for autophagy occurs in cancer cells and how mitochondrial metabolic reprogramming in cancer cells can activate autophagy through PKA regulation. However, the requirement of mitochondrial activity for autophagy has been demonstrated also in mammalian cells and involves mitochondrial phospholipid remodelling (see section Mitochondrial-Associated ER Membranes) [63].

Autophagy is highly regulated by the presence or absence of metabolic substrates in the microenvironment. Therefore, several signalling pathways controlled by substrate availability in the tumour microenvironment, including glutamine, lactate or fatty acids have been associated with autophagy. Glutamine and leucine metabolism is linked with amino acid sensing via the lysosomes and mTORC1. The production of α-ketoglutarate through glutaminolysis has been demonstrated to be a major component of the amino acid sensing and of autophagy regulation. Indeed α-ketoglutarate is necessary for the activity of the EGLNs/prolyl hydroxylases, leading to the activation of the small GTPase RRAGB and subsequent translocation and activation of mTORC1 to the lysosome and inhibition of autophagy [64-66]. In cancer cells, the long term activation of glutaminolysis in condition of amino acid restriction induces the activation of mTORC1, represses autophagy and

activates apoptosis [67]. However the role of glutamine metabolism in autophagy regulation is complex. Besides fuelling the TCA cycle with α-ketoglutarate, glutaminolysis produces ammonia which has long been considered as a by-product before the discovery of its role in autophagy [68]. Although the mechanism is not clearly understood, ammonia activates autophagy through AMPK and the unfolded-protein response system independently of mTOR [69]. Ammonia is found in tumours at high concentration in the interstitial fluid [68]. Because ammonia is diffusible, it is proposed that glutaminolysis-derived ammonia activates autophagy even in the hypoxic core of the tumour as an adaptation mechanism to protect against cell death in condition of metabolic stress [70]. Furthermore, ammonia is at the basis of a self-fuelling system between cancer-associated fibroblasts (CAF) and cancer cells. The glutamine produced by CAF is imported in epithelial cancer cells to fuel the TCA cycle after its conversion to glutamate and α-ketoglutarate, while the ammonia produced diffuses and activates autophagy in CAF [71].

Another particular adaptation of cancer cells which depends on autophagy is the metabolic symbiosis based on lactate exchanges between glycolytic, lactate-producing cells, and oxidative, lactate-consuming cells. These lactate exchanges have been described between cancer cells from different metabolic phenotypes [4] and between cancer cells and fibroblasts [72]. This cooperation requires the entry of lactate into the oxidative cells, a process facilitated by the lactate-proton symporter monocarboxylate transporter type 1 (MCT1), and its oxidation to pyruvate by lactate dehydrogenase B (LDHB). In oxidative cancer cells, lactate is used for OXPHOS [4] and for the production of lipids [73]. Interestingly the oxidation of lactate by LDHB also participates to lysosome function and activates autophagy in cancer cells [28]. The activation of autophagy by lactate utilisation promotes cancer cell survival and tumour growth whereas it has no effect on autophagy and the survival of non-cancer cells [28].

In cancer cells, fatty acid (FA) metabolism is central to cancer progression since FA synthesis provides building blocks and FA oxidation (FAO) is an important energy source [74]. The relationship between FA and autophagy is not clearly understood, and both activation and inhibition of FAO have been associated to autophagy. In prostate cancer cells, the inhibition of FAO using etomoxir (Carnitine PalmitoylTransferase I inhibitor) activates autophagy through the activation of AMPK and inhibition of mTOR [75]. On the opposite, in colon cancer cells, the activation of FAO activates autophagy through the activation of AMPK and promotes tumour growth [76]. In this model, surrounding adipocytes provide cancer cells with FA to fuel FAO and promote survival under low nutrient conditions [76]. Bone marrow adipocytes can also activate FAO and AMPK in acute leukaemia cells, leading to autophagy activation [77]. This relation of tumours with the surrounding adipose tissue is particularly important for cancer progression and may potentially limit cancer treatment.

Furthermore, the relation of lipid metabolism and autophagy is complex because reciprocally, autophagy can provide FA for FAO [78].

1.3.2.Reactive Oxygen Species

Mitochondria is the major source of ROS. An elevated level of ROS is an important feature of cancer cells, and could be attributed to mitochondrial electron transport chain activity (mainly Complex I and Complex III). Increased ROS production by mitochondria in cancer cells is associated with metastasis through the activation of Src and the Focal adhesion kinase Pyk2 [12]. Although a massive ROS generation is mainly associated with cell damage and cell death, moderate ROS production is known to activate autophagy through multiple pathways. Autophagy is activated by ROS through the activation of the sensor Ataxia-telangiectasia mutated (ATM) leading to mTORC1 inhibition through the LKB1/AMPK/TSC2 pathway [79]. Oxidative stress can also induce autophagy through an NFkB-dependent upregulation of p62 [80]. Furthermore, ROS production is involved in starvation-induced autophagy [81]. During nutrient starvation, the ROS produced regulates the activity of the HsAtg4 protease, which is important for phosphatidylethanolamine (PE) conjugation to LC3 [81]. Mitochondrial ROS can also regulate autophagy through oxidation of lysosomal membrane proteins and modulation of Ca^{2+} homeostasis [82, 83]. The activation of TRPML1, a lysosomal Ca^{2+}-permeable transient Receptor Potential (TRP) channel, by ROS induces lysosomal Ca^{2+} release, followed by the activation of calcineurin signalling, TFEB nuclear translocation and activation of autophagy and lysosome biogenesis [82]. On the opposite, the activation of the lysosomal Ca^{2+} channel TRPM2 by ROS induces Ca^{2+} CaMKII signalling, leading to autophagy inhibition [83]. Among ROS species, it has been proposed that superoxide $O2^{\bullet-}$ is the major regulator of autophagy since superoxide production induced by the dysfunction of mitochondrial complexes I and III activates autophagy [84].

Although the mechanisms are not clearly described, elevated ROS production caused by dysfunction of mitochondria can participate to the regulation of autophagy in tumours, and consequently to cancer progression. ROS are produced during extracellular matrix detachment, which is an important step for metastatic dissemination [85, 86]. It has been demonstrated that ROS production during matrix detachment promotes autophagy through the activation of PERK1 and promotes anoikis resistance [87]. Interestingly active PERK1 and LC3 are increased in human breast ductal carcinoma compared to normal breast suggesting an important role of this signalling pathway during cancer progression [87]. ROS are also produced following anticancer treatments such as chemo and radio-therapies [88]. Although ROS play an important part for the mechanism of action of these anticancer treatments, the activation of autophagy by ROS could participate to cancer cell survival and therapy resistance. This has been demonstrated in bladder cancer cells in which the oxidative stress induced

by capsaicin activates autophagy as a pro-survival mechanism promoting drug resistance [89]. In lung adenocarcinoma, ROS induced by low dose radiations promote autophagy and confer radio-resistance [90].

1.3.3.Mitochondrial-Associated ER Membranes (MAM)

The juxtaposition of membranes from the ER and mitochondria, including specific proteins, forms a subdomain called MAM (Figure 1). This interface plays an important role for ion and lipid exchanges between mitochondria and ER allowing the proper function of the two organelles [91]. Mitochondrial membranes and MAM have been suggested to participate to autophagosome formation as lipid source. The first evidence that mitochondrial membrane participates to autophagosome formation came from the identification of phospholipid transfers from mitochondria to autophagosome in starved cells [92]. The role of MAM in autophagosome formation seems to involve the conversion of phosphatidylserine (PS) from the ER to phosphatidylethanolamine (PE) by inner mitochondrial membrane (IMM) phosphatidylserine decarboxylase [63], allowing PE-LC3 conjugation, and autophagy [93]. It has recently been demonstrated that the activation of autophagy by mTOR inhibition induced an increase in MAM formation and the remodelling of the mitochondrial membrane phospholipids, with an increase in PS and PE [63]. Interestingly, the activity of complex I is required for MAM formation, phospholipid remodelling and autophagy [63].

On the other hand, some studies showed that the disruption of MAM activates autophagy. MAM are important sites for the transfer of Ca^{2+} from the ER to the mitochondria to regulate mitochondrial enzymes as respiratory complexes and TCA cycle enzymes. This Ca^{2+} flux occurs mainly through IP3 Receptor and TRPM8 in the ER membrane [94, 95] and through the Voltage-Dependent Anion Channel (VDAC), the Mitochondrial Calcium Uniporter (MCU) and the Transient Receptor Protein Melastatin-related 2 (TRPM2) in the mitochondrial membranes [96, 97] (See section ”mitochondrial calcium transporters as a new target for autophagy/mitophagy modulation”). The interruption of Ca^{2+} flux between the ER and mitochondria decreases OXPHOS, induces metabolic stress and activates autophagy as a survival mechanism [94]. However, the activation of autophagy by MAM disruption in cancer cells does not seem sufficient, unlike in normal cells, to maintain the energetic level needed, thus leading to cancer cell death and decrease in tumour growth [98]. Furthermore, tightening ER-mitochondria contact sites can inhibit rapamycin-induced autophagy but not starvation-induced autophagy suggesting that MAM play different roles depending on autophagy stimuli [99].

Several oncoproteins and tumour suppressor proteins have been identified in MAM, which highlighted the complex relationships between these structures and cancer progression. Indeed,

MAM is now proposed to play an important role in cancer metabolism and growth [100]. However, the alterations of MAM formation or architecture in cancer are not clearly understood. Although still controversial, the recent association of MAM with autophagy regulation might be responsible for their important roles in cancer. Pharmacological intervention could be a strategy to disrupt MAM and inhibit both mitochondrial metabolism and autophagy [63]. A better understanding of the involvement of MAM in cancer progression and its involvement in the regulation of autophagy is needed to propose new targeted therapies.

Altogether these studies highlight the complex regulation of autophagy by mitochondrial metabolism in tumours. On the one hand autophagy is activated by metabolic changes linked with a decrease in ATP production but also by ammonia production, ROS and interruption of Ca^{2+} transfers in MAM. On the other hand recent evidences suggest that mitochondrial function participates to autophagy induction as a lipid source or through the activation of PKA. Since mitochondria and autophagy are important players of cancer progression and resistance to treatment, it is crucial to better understand their mutual regulations. Therefore more studies are needed to clarify the regulation of autophagy by mitochondria in different tumour types and during tumorigenesis. Furthermore, the tumour microenvironment is much more complex than what can be reproduced in *in vitro* cell culture models: it contains various cell types like cancer-associated fibroblasts, adipocytes, immune cells, as well as gradients for oxygen and metabolites. All of these features of the tumours microenvironment require being assessed *in vivo*. Interestingly the microenvironment of tumours can also play a role in autophagy regulation in cancer cells by providing lactate, glutamine or FA and by regulating tumour-stroma interaction [34, 35]. Therefore it is important to clarify the effects of metabolic drugs on autophagy in tumours and to consider their association with autophagy inhibitors.

2. Targeting mitophagy in cancer

2.1. Mitophagy regulation and function

Mitochondrial mass is highly dynamic and tightly regulated through fusion/fission, but also by mitobiogenesis and mitophagy. Mitophagy is a specific form of autophagy that selectively degrades mitochondria through PINK1/Parkin and BNIP3/NIX/FUNDC1 pathways. It is triggered by mitochondrial depolarization, hypoxia and metabolic stress. The PINK1/Parkin pathway has been originally identified in Parkinson's disease where mutations in corresponding genes impair mitochondrial clearance. The activation of mitophagy by membrane depolarization involves the mitochondrial kinase PINK1, the localisation of which depends on mitochondrial membrane potential

[101]. In normal conditions, the voltage-dependent translocation of PINK1 to the IMM induces its cleavage by the mitochondrial protease PARL. When IMM is depolarized, PINK1 accumulates in the outer mitochondrial membrane (OMM) where it phosphorylates the E3 ubiquitin ligase Parkin, leading to its recruitment at the OMM [102]. Several mitochondrial proteins, including VDAC1, Miro, Mfn-1 and Mfn-2, are ubiquitinylated by Parkin [103] and recognized by LC3-interacting proteins p62, NDP52, optineurin, TAX1BP1 or NBR-1 to recruit the autophagic machinery [104-108]. Mitophagy is also activated by hypoxia through the induction of adaptor proteins: BNIP3, NIX (or BNIP3L) and FUNDC1. These proteins are localized in the OMM and contain an LC3-interacting motif to promote the recruitment of the autophagic machinery [109]. The expression of BNIP3 and NIX is increased by hypoxia through Hypoxia-inducible factor (HIF-1) [110, 111] whereas FUNDC1 is dephosphorylated in hypoxia by Src kinase inactivation, increasing its affinity for LC3 compared to phosphorylated FUNDC1 [112]. In addition, AMPK activation by low nutrient availability can directly activate mitophagy through phosphorylation of Ulk1 [20].

Besides the activation of PINK1/Parkin and BNIP3/NIX/FUNDC1 pathways, mitophagy is highly linked to mitochondrial function, enabling to equilibrate mitochondrial degradation with mitochondrial activity requirement. Mitophagy is activated by OXPHOS activity to stimulate the renewal of mitochondria and maintain their efficiency [113]. In addition, mitophagy induces the translocation of Nrf2 and TFEB transcription factors to the nucleus, inducing the transcription of autophagy, lysosome and mitochondria-related genes to renew lysosomal and mitochondrial compartments [114]. Furthermore, the recognition of injured mitochondria for degradation through mitophagy is regulated by mitochondrial membrane composition. In normal condition, cardiolipins, specific mitochondrial phospholipids, are mostly located in the IMM. Cardiolipin externalization to the OMM leads to its interaction with LC3 and acts as an elimination signal for mitophagy [115]. The hexameric intermembrane space protein, NDPK-D, has been identified as the cardiolipin translocation system, in case of mitochondrial depolarisation, which is needed for the elimination of damaged mitochondria by mitophagy [116].

Mitophagy cooperates with mitochondrial dynamic and it is now admitted that mitochondrial fission precedes mitophagy. The mitophagy proteins Parkin and BNIP3 interact with the mitochondrial fission factor dynamin-related protein (Drp) 1 [117, 118]. This cooperation is further enhanced in hypoxia with the recruitment of FUNDC1 in MAM due to its interaction with the ER protein calnexin, leading to the recruitment of Drp1 to allow mitochondrial fission and mitophagy [119]. Furthermore, during mitophagy induction, PINK1 and Beclin1 relocalize to the MAM and promote autophagosome formation [120].

2.2. Mitophagy in cancer

Because mitophagy can degrade dysfunctional mitochondria and limit ROS production, its function has been associated with tumour suppression. Indeed, Parkin or PINK1 deletion in mice leads to the spontaneous development of hepatocellular carcinoma [121] and increases Kras-driven pancreatic tumorigenesis [122]. In human, Parkin deletion has been identified in tumours including colorectal cancer [123], glioblastoma [124], melanoma [125], lung cancer [126] and breast cancer [127, 128]. Loss of Parkin increases proinflammatory signals, promotes genomic instability [126], increases cancer cell proliferation and resistance to apoptosis [121, 125]. Interestingly the accumulation of mitochondrial dysfunctions induced by Parkin deficiency decreases mitochondrial OXPHOS, increases ROS production and increases glycolysis, therefore possibly contributing to the Warburg effect, and consequently increases tumorigenesis [129]. Furthermore, Parkin has been identified as an E3 ubiquitin ligase for HIF-1α to promote its proteasomal degradation. Therefore, the downregulation of Parkin in breast cancer cells stabilizes HIF-1α and promotes metastasis [130]. The BNIP3 pathway has also been linked with a tumour suppression function of mitophagy. A decrease of BNIP3 is found in pancreatic cancers and associated with chemoresistance and poor prognosis [131, 132]. In mammary tumours, BNIP3 decreases with cancer progression, leading to an accumulation of mitochondria associated with an increase ROS production and HIF-1α stabilization [133]. The authors demonstrated that the loss of BNIP3 promotes mammary tumour growth, progression to metastasis and can be used as a prognostic marker in human triple-negative breast cancer [133]. Lastly, FUNDC1-deficient mice showed an increase in tumour initiation, also suggesting a tumour suppressor role for FUNDC1 [134]. Altogether, these studies highlighted the role of mitophagy as a tumour suppressor and the potential benefit of its induction to limit the consequences of mitochondrial dysfunction in cancer.

Like non-selective autophagy, the role of mitophagy is complex and can depend on tumour type and stage. Although mitophagy has been associated with tumour suppression in early stages of the tumour development, it can promote tumour growth at advanced stages. Indeed, mitophagy can be induced when AMPK is activated by low nutrient conditions [20], a condition found in tumours. Hypoxia, a common feature of solid tumours, has been shown to activate mitophagy in cancer cells through BNIP3 and NIX induction [110]. Furthermore, the induction of mitophagy depends on mitochondrial metabolism, such as glutamine availability and use which can increase BNIP3 expression and mitophagy in melanoma cells [135]. While few studies investigated mitophagy in tumours, its activity seems dependent on tumour metabolism and microenvironment.

In several cancer types, the degradation of damaged mitochondria and the recycling of metabolic precursors by mitophagy can promote cell survival and protect from cell death [110] [136]. In Parkin-deficient mice melanoma growth and metastasis are suppressed, suggesting a pro-tumour role of Parkin-dependent mitophagy [137]. However, Parkin is often downregulated in many tumour types. It has been recently demonstrated that besides this frequent loss of parkin, PINK1-dependent mitophagy can be functional through the induction of the E3 ubiquitin ligase ARIH1/HHAR [138]. Interestingly ARIH1 is overexpressed in breast and lung cancer cells while Parkin expression is low [138]. In addition, BNIP3 induction has been reported to promote cell migration through cytoskeleton remodelling [139], resistance to anoikis [140] and invasion [141], suggesting a role of BNIP3-dependent mitophagy in metastasis formation. The pro-survival role of mitophagy has also been associated with resistance to anti-cancer treatments, such as the ARIH1-PINK1 mitophagy which protects against cisplatin-induced cell death [138]. A role of mitophagy in resistance to anti-cancer treatment is also suggested in a study showing that doxorubicin induces the expression of NIX in cancer stem cells and promotes resistance to treatment through limitation of ROS production [142]. Interestingly, FUNDC1 silencing has been proposed to improve chemotherapy efficiency by increasing cisplatin-induced cell death [143].

Consistently with the dual role of mitophagy in cancer progression, the expression of mitophagy proteins has been found to be either downregulated or overexpressed in different cancer types. BNIP3 has been found downregulated in invasive ductal carcinoma and metastases [144] and in pancreatic cancers [131, 132] but upregulated in breast ductal carcinoma *in situ* [145] and in other human cancer tissues (ovarian, head and neck squamous cell carcinoma) where BNIP3 localized in perinecrotic regions [111]. It has been suggested that some of these mitophagy proteins can be used as prognosis markers in specific cancers. A high expression of FUNDC1 has been associated with poor prognosis in cervical cancer [143]. High BNIP3 expression can be used as a prognosis marker in specific cancers such as uveal melanoma where a high BNIP3 expression is associated with a poor prognosis [146]. However, there is a controversy concerning the role of BNIP3-dependent mitophagy in cancer that could be explained by an alternatively spliced BNIP3 expressed preferentially in cancer cells: whereas the full-length BNIP3 promotes cell death, the Bnip3Δex3 isoform promotes cell survival [147]. Interestingly, a switch towards a glycolytic metabolism increases the expression of the Bnip3Δex3 isoform [147].

Altogether, these studies highlighted the complex role of mitophagy in cancer progression, showing either pro-tumour or anti-tumour activities depending on tumour type, stage, or its metabolic activity. However, recent evidence suggest an important role of mitophagy in tumour growth, metastasis and therapy resistance. Since mitophagy is an important regulator of mitochondrial

number and function, its pharmacological modulation in tumours could be a promising anticancer strategy. However, the proposition of mitophagy inhibition or activation is limited by the little knowledge of its role and regulation in preclinical models and in human tumours. Therefore, a major challenge will be to identify the specific roles of the different mitophagy pathways in human cancers before being able to propose mitophagy modulators for anti-cancer therapy. The identification of mitophagy biomarkers will be helpful to design mitophagy modulators for tumours having a high requirement for mitophagy. It is important to clarify the role of mitophagy in tumours and to investigate the effect of its modulation in tumour-bearing mice models to reflect the behaviour of tumours detected in patients. It is also important to develop specific tools to modulate mitophagy *in vivo* and not using general autophagy inhibitors. This issue could be addressed using mitochondrial targeted molecules, for example using triphenylphosphonium derivatives structures [148], to deliver autophagy inhibitors. Interestingly using this strategy with mitochondria-targeted redox agents can activate mitophagy selectively in breast cancer cells compared to non-cancer cells [149].

3. Mitochondrial calcium transporters as new targets for autophagy / mitophagy modulation

The OXPHOS activity leads to a strong proton concentration in the intermembrane space (IMS) and is the main factor that determines the very negative voltage (Ψm) of the IMM. Therefore the modulation of OXPHOS activity can influence the proton gradient and consequently the IMM potential. The electrochemical gradient in the IMS is favourable to cation influx (mainly K^+ and Ca^{2+}) into the mitochondrial matrix and regulates the activity of mitochondrial enzymes, ROS and ATP production. This cation fluxes is tightly regulated by the expression of ion channels in the IMM: BK_{Ca}, K_{ATP}, Kv1.3, MCU, SK-family members, TRP-family members, CLIC4 and others, while the main actor in the OMM that allows ion flux is VDAC [96, 97, 150, 151] (Figure 1). An interruption of cation fluxes decreases OXPHOS activity and on the opposite a high cation influx induces mitochondrial membrane depolarization [152, 153]. Since autophagy and mitophagy are linked with mitochondrial function, the modulation of mitochondrial ion channels could be an interesting strategy to modulate autophagy or mitophagy in tumours. Indeed, mitochondrial depolarization induces mitophagy through the PINK1/Parkin pathway [101, 102] and the disruption of mitochondrial potential by FCCP and CCCP activates autophagy and mitophagy through Nrf2 pathway and TFEB transcription factor [154]. Therefore the inhibition of cation flux could have a dual effect in reducing mitochondrial function but also mitophagy by preventing mitochondrial depolarization.

399 Among cations, Ca^{2+} exchanges have been associated with autophagy and mitophagy regulation.
400 VDAC is the most abundant protein in the OMM, and is ubiquitously expressed in all eukaryotic cells.
401 In its open state it becomes an aspecific pore, allowing the flux of many substrates and ions smaller
402 than 5 kDa. In this condition, VDAC is highly Ca^{2+} permeable and allows Ca^{2+} flux to IMS, thus
403 modulating Ca^{2+} availability to Ca^{2+} permeant-channels in the IMM. MCU is a Ca^{2+} channel present in
404 the IMM, ubiquitously expressed and generally considered as the main Ca^{2+} transporter in the matrix.
405 Two pools of calcium can be imported into the mitochondria: one from the cytosol and another one
406 from the ER. The juxtaposition of ER and mitochondria in MAM facilitates the generation of a high
407 Ca^{2+} concentration that could be efficiently transferred to mitochondrial compartments. This Ca^{2+} flux
408 in MAM has important roles for the regulation of mitochondrial function since its interruption
409 decreases OXPHOS and activates autophagy [94] [98]. On the opposite, the disruption of MAM has
410 been associated with a decrease in mitochondrial PE production and therefore a reduction of
411 autophagy [63]. Although the mechanisms linked with autophagy are not clearly understood, VDAC
412 and MCU could be interesting targets to disrupt Ca^{2+} and lipid exchanges in MAM in cancer cells,
413 decreasing mitochondrial function and inducing cell death. Furthermore, VDAC is involved in Parkin
414 recruitment to defective mitochondria, triggering mitophagy [155]. The Ca^{2+} fluxes in MAM through
415 MCU is also important for Parkin-dependent mitophagy [156]. Because of their double role in
416 mitochondrial Ca^{2+} flux and Parkin recruitment, VDAC and MCU could be used to target mitophagy
417 and autophagy regulation in tumours. VDAC is overexpressed in several tumour types and pre-clinical
418 models, suggesting that it could be an interesting anticancer target [157, 158]. Although the
419 mechanism has not been linked to autophagy, VDAC downregulation decreases mitochondrial
420 membrane potential, cellular ATP content, cancer cell migration, proliferation and tumour growth in
421 lung cancer xenografts [159]. MCU has also been found to be altered in tumours from different
422 tissues [160]. In particular, in human breast [161, 162] and hepatocellular [163] carcinomas, the
423 expression of MCU is associated with cancer progression and metastasis.

424 The MCU regulator 1 (MCUR1) is a secondary subunit of MCU complex allowing ion flux into the
425 matrix [164, 165]. MCUR1 downregulation decreases Ca^{2+} flux, OXPHOS, ATP production and
426 activates AMPK-dependent autophagy [164, 165]. MCUR1 is upregulated in hepatocellular carcinoma
427 and its expression is associated with cancer cell survival and tumour growth [166]. In this model,
428 MCUR1 induces mitochondrial Ca^{2+} accumulation and ROS production, showing that MCUR1
429 association with MCU is necessary for a functional MCU complex and its Ca^{2+}-associated entry into
430 mitochondria is a pro-survival factor for cancer cells [166].

431 Several other ion channels have been identified in the IMM of different cell type and could
432 compensate for MCU-dependent Ca^{2+} flux. Among them, two splice variants of TRPM2 are expressed

in neuroblastoma. The functional TRPM2-L and the dominant negative TRPM2-S are both localized in mitochondria [167]. In xenograft models of SH-SY5Y glioblastoma cell line, the expression of the dominant negative isoform decreases mitophagy and led to smaller tumour growth, showing that a functional mitochondrial TRPM2 is necessary for mitophagy and cancer growth [167]. In this model, TRPM2-S was associated with a reduction in HIF-1/2α and BNIP3 expression [167]. The role of mitochondrial TRMP2 in mitophagy has also been demonstrated in gastric cancer cell lines where the downregulation of TRPM2 decreases mitochondrial oxygen consumption and ATP production associated with a reduction in mitophagy and autophagy through a JNK-dependent and mTOR-independent pathway [168]. The reduction of mitophagy and autophagy by the lack of functional TRPM2 is also associated with enhanced efficacies of doxorubicin, tamoxifen and paclitaxel chemotherapies, showing the potential benefit of targeting mitochondrial TRPM2 for cancer therapies [167-169]. Interestingly, TRPM2 inhibition or silencing did not increase doxorubicin cytotoxicity in non-cancerous HMEC cell line [169].

Conclusion

Altogether, these studies highlighted the complex relation between mitochondria (ATP and ROS production, MAM and calcium transporters) and autophagy. Autophagy could result, as a metabolic adaptation, from chemotherapies targeting mitochondria. In this context, targeting both autophagy and mitochondria could limit chemoresistance mechanisms. However, recent discoveries suggest that mitochondria are also involved in autophagic activity, mainly by providing lipids for autophagosome formation. Because of these two effects on autophagy, mitochondria could be considered as a target for cancer therapy. Mitophagy seems to play an important role in cancer cells, but its effects on cancer cell growth could be different depending on carcinogenesis stage and cancer types. Therefore, mitophagy modulation could be beneficial for metastasis prevention and improve therapy efficacy. Among mitochondrial proteins, calcium transporters have a key role in the regulation of mitochondrial function. These mitochondrial calcium transporters have been recently associated with autophagy and mitophagy regulation in cancer cells. Consequently they also represent attractive anticancer targets to modulate mitochondrial dysfunction and autophagy/mitophagy in tumours. Studies are still needed to better understand the regulations of autophagy and mitophagy by cancer metabolism, and develop strategies targeting both cancer metabolism and autophagy to avoid adaptation and resistance mechanisms.

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Conflict of interests

Authors declare no conflict of interest.

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Figure legend

Figure 1: Regulation of autophagy and mitophagy by cancer cell metabolism. Cancer cells use a wide range of metabolic substrates including glucose (blue arrows), lactate, fatty acids (green arrows) and glutamine (orange arrows) to sustain the production of ATP and intermediate precursors for nucleotides, fatty acids (FA) and amino acids (aa) synthesis needed for proliferation. Autophagy and mitophagy are highly regulated by nutrients availability and reprogrammed metabolic pathways used by cancer cells. When ATP production is sufficient, the inactivation of AMPK pathway represses autophagy and mitophagy. The production of α-ketoglutarate (α-KG) through glutaminolysis is a major component of aa sensing and of autophagy repression under high substrate availability. However, ammonia, lactate and reactive oxygen species (ROS) production are associated with autophagy activation. Fatty acid oxidation (FAO) can either activate or repress autophagy. Mitochondria are also involved in autophagy regulation through the formation of Mitochondria-Associated endoplasmic reticulum (ER) Membrane (MAM) subdomains which are important for ion and lipid (particularly phosphatidylserine, PS) exchanges between mitochondria and ER. On the one hand, MAM formation and the remodelling of mitochondrial membrane phospholipids, with production of phosphatidylethanolamine (PE) and subsequent LC3-PE promotes autophagy. On the other hand, the entry of $Ca2^{+}$ from the cytosol and from the ER in MAM allows the proper functioning of mitochondrial enzymes and therefore represses autophagy. Similarly, the specific recycling of mitochondria by mitophagy is repressed by the maintenance of Ca^{2+} flux in mitochondria and by sustained ATP production. However, mitochondrial calcium channels voltage-dependent anion channel (VDAC), transient receptor potential channel M2 (TRPM2) and mitochondrial calcium uniporter (MCU) are involved in mitophagy activation by the protein Parkin or by hypoxia. In normal conditions, cardiolipins, specific mitochondrial phospholipids, are mostly located in the inner

mitochondrial membrane (IMM). Cardiolipin externalization to the outer mitochondrial membrane (OMM) leads to its interaction with LC3 and acts as an elimination signal for mitophagy. Yellow pointed arrows (---->) represent a stimulation of mitophagy or autophagy. Yellow blunt-end arrows represent a repression or inhibition (----I) of mitophagy or autophagy. AcCoA is for acetyl-coenzyme A. IMS is for inter membrane space, limited by the OMM and IMM. OXPHOS is for mitochondrial oxidative phosphorylation. TCA cycle is for tricarboxylic acid cycle.

1. Warburg, O., *On the origin of cancer cells.* Science, 1956. **123**(3191): p. 309-14.
2. Moreno-Sanchez, R., S. Rodriguez-Enriquez, A. Marin-Hernandez, and E. Saavedra, *Energy metabolism in tumor cells.* FEBS J, 2007. **274**(6): p. 1393-418.
3. DeBerardinis, R.J. and T. Cheng, *Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer.* Oncogene, 2010. **29**(3): p. 313-24.
4. Sonveaux, P., F. Vegran, T. Schroeder, M.C. Wergin, J. Verrax, Z.N. Rabbani, C.J. De Saedeleer, K.M. Kennedy, C. Diepart, B.F. Jordan, M.J. Kelley, B. Gallez, M.L. Wahl, O. Feron, and M.W. Dewhirst, *Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice.* J. Clin. Invest, 2008. **118**(12): p. 3930-3942.
5. Nieman, K.M., H.A. Kenny, C.V. Penicka, A. Ladanyi, R. Buell-Gutbrod, M.R. Zillhardt, I.L. Romero, M.S. Carey, G.B. Mills, G.S. Hotamisligil, S.D. Yamada, M.E. Peter, K. Gwin, and E. Lengyel, *Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth.* Nat Med, 2011. **17**(11): p. 1498-503.
6. Vander Heiden, M.G., L.C. Cantley, and C.B. Thompson, *Understanding the Warburg effect: the metabolic requirements of cell proliferation.* Science, 2009. **324**(5930): p. 1029-33.
7. Hosios, A.M., V.C. Hecht, L.V. Danai, M.O. Johnson, J.C. Rathmell, M.L. Steinhauser, S.R. Manalis, and M.G. Vander Heiden, *Amino Acids Rather than Glucose Account for the Majority of Cell Mass in Proliferating Mammalian Cells.* Dev Cell, 2016. **36**(5): p. 540-9.
8. Hsu, C.C., L.M. Tseng, and H.C. Lee, *Role of mitochondrial dysfunction in cancer progression.* Exp Biol Med (Maywood), 2016. **241**(12): p. 1281-95.
9. Porporato, P.E., N. Filigheddu, J.M.B. Pedro, G. Kroemer, and L. Galluzzi, *Mitochondrial metabolism and cancer.* Cell Res, 2018. **28**(3): p. 265-280.
10. Zong, W.X., J.D. Rabinowitz, and E. White, *Mitochondria and Cancer.* Mol Cell, 2016. **61**(5): p. 667-676.
11. Dumas, J.F., L. Brisson, S. Chevalier, K. Maheo, G. Fromont, D. Moussata, P. Besson, and S. Roger, *Metabolic reprogramming in cancer cells, consequences on pH and tumour progression: Integrated therapeutic perspectives with dietary lipids as adjuvant to anticancer treatment.* Semin Cancer Biol, 2017. **43**: p. 90-110.
12. Porporato, P.E., V.L. Payen, J. Perez-Escuredo, C.J. De Saedeleer, P. Danhier, T. Copetti, S. Dhup, M. Tardy, T. Vazeille, C. Bouzin, O. Feron, C. Michiels, B. Gallez, and P. Sonveaux, *A mitochondrial switch promotes tumor metastasis.* Cell Rep, 2014. **8**(3): p. 754-766.
13. Weinberg, S.E. and N.S. Chandel, *Targeting mitochondria metabolism for cancer therapy.* Nat Chem Biol, 2015. **11**(1): p. 9-15.
14. Zhu, Y., A.E. Dean, N. Horikoshi, C. Heer, D.R. Spitz, and D. Gius, *Emerging evidence for targeting mitochondrial metabolic dysfunction in cancer therapy.* J Clin Invest, 2018. **128**(9): p. 3682-3691.
15. Ichimura, Y., T. Kirisako, T. Takao, Y. Satomi, Y. Shimonishi, N. Ishihara, N. Mizushima, I. Tanida, E. Kominami, M. Ohsumi, T. Noda, and Y. Ohsumi, *A ubiquitin-like system mediates protein lipidation.* Nature, 2000. **408**(6811): p. 488-92.
16. Mizushima, N., T. Noda, T. Yoshimori, Y. Tanaka, T. Ishii, M.D. George, D.J. Klionsky, M. Ohsumi, and Y. Ohsumi, *A protein conjugation system essential for autophagy.* Nature, 1998. **395**(6700): p. 395-8.
17. Zaffagnini, G. and S. Martens, *Mechanisms of Selective Autophagy.* J Mol Biol, 2016. **428**(9 Pt A): p. 1714-24.
18. Hosokawa, N., T. Hara, T. Kaizuka, C. Kishi, A. Takamura, Y. Miura, S. Iemura, T. Natsume, K. Takehana, N. Yamada, J.L. Guan, N. Oshiro, and N. Mizushima, *Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy.* Mol Biol Cell, 2009. **20**(7): p. 1981-91.
19. Jung, C.H., C.B. Jun, S.H. Ro, Y.M. Kim, N.M. Otto, J. Cao, M. Kundu, and D.H. Kim, *ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery.* Mol Biol Cell, 2009. **20**(7): p. 1992-2003.

20. Egan, D.F., D.B. Shackelford, M.M. Mihaylova, S. Gelino, R.A. Kohnz, W. Mair, D.S. Vasquez, A. Joshi, D.M. Gwinn, R. Taylor, J.M. Asara, J. Fitzpatrick, A. Dillin, B. Viollet, M. Kundu, M. Hansen, and R.J. Shaw, *Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy.* Science, 2011. **331**(6016): p. 456-61.
21. Kim, J., M. Kundu, B. Viollet, and K.L. Guan, *AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1.* Nat Cell Biol, 2011. **13**(2): p. 132-41.
22. Kim, K.H. and M.S. Lee, *Autophagy--a key player in cellular and body metabolism.* Nat Rev Endocrinol, 2014. **10**(6): p. 322-37.
23. Mizushima, N. and M. Komatsu, *Autophagy: renovation of cells and tissues.* Cell, 2011. **147**(4): p. 728-41.
24. Rao, S., L. Tortola, T. Perlot, G. Wirnsberger, M. Novatchkova, R. Nitsch, P. Sykacek, L. Frank, D. Schramek, V. Komnenovic, V. Sigl, K. Aumayr, G. Schmauss, N. Fellner, S. Handschuh, M. Glosmann, P. Pasierbek, M. Schlederer, G.P. Resch, Y. Ma, H. Yang, H. Popper, L. Kenner, G. Kroemer, and J.M. Penninger, *A dual role for autophagy in a murine model of lung cancer.* Nat Commun, 2014. **5**: p. 3056.
25. White, E., *The role for autophagy in cancer.* J Clin Invest, 2015. **125**(1): p. 42-6.
26. Yue, Z., S. Jin, C. Yang, A.J. Levine, and N. Heintz, *Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor.* Proc Natl Acad Sci U S A, 2003. **100**(25): p. 15077-82.
27. Qu, X., J. Yu, G. Bhagat, N. Furuya, H. Hibshoosh, A. Troxel, J. Rosen, E.L. Eskelinen, N. Mizushima, Y. Ohsumi, G. Cattoretti, and B. Levine, *Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene.* J Clin Invest, 2003. **112**(12): p. 1809-20.
28. Brisson, L., P. Banski, M. Sboarina, C. Dethier, P. Danhier, M.J. Fontenille, V.F. Van Hee, T. Vazeille, M. Tardy, J. Falces, C. Bouzin, P.E. Porporato, R. Frederick, C. Michiels, T. Copetti, and P. Sonveaux, *Lactate Dehydrogenase B Controls Lysosome Activity and Autophagy in Cancer.* Cancer Cell, 2016. **30**(3): p. 418-31.
29. Papandreou, I., A.L. Lim, K. Laderoute, and N.C. Denko, *Hypoxia signals autophagy in tumor cells via AMPK activity, independent of HIF-1, BNIP3, and BNIP3L.* Cell Death Differ, 2008. **15**(10): p. 1572-81.
30. Poillet-Perez, L., G. Despouy, R. Delage-Mourroux, and M. Boyer-Guittaut, *Interplay between ROS and autophagy in cancer cells, from tumor initiation to cancer therapy.* Redox Biol, 2015. **4**: p. 184-92.
31. Maiuri, M.C., E. Tasdemir, A. Criollo, E. Morselli, J.M. Vicencio, R. Carnuccio, and G. Kroemer, *Control of autophagy by oncogenes and tumor suppressor genes.* Cell Death Differ, 2009. **16**(1): p. 87-93.
32. Strohecker, A.M., J.Y. Guo, G. Karsli-Uzunbas, S.M. Price, G.J. Chen, R. Mathew, M. McMahon, and E. White, *Autophagy sustains mitochondrial glutamine metabolism and growth of BrafV600E-driven lung tumors.* Cancer Discov, 2013. **3**(11): p. 1272-85.
33. Guo, J.Y., X. Teng, S.V. Laddha, S. Ma, S.C. Van Nostrand, Y. Yang, S. Khor, C.S. Chan, J.D. Rabinowitz, and E. White, *Autophagy provides metabolic substrates to maintain energy charge and nucleotide pools in Ras-driven lung cancer cells.* Genes Dev, 2016. **30**(15): p. 1704-17.
34. Maes, H., N. Rubio, A.D. Garg, and P. Agostinis, *Autophagy: shaping the tumor microenvironment and therapeutic response.* Trends Mol Med, 2013. **19**(7): p. 428-46.
35. Mowers, E.E., M.N. Sharifi, and K.F. Macleod, *Functions of autophagy in the tumor microenvironment and cancer metastasis.* FEBS J, 2018. **285**(10): p. 1751-1766.
36. Lazova, R., R.L. Camp, V. Klump, S.F. Siddiqui, R.K. Amaravadi, and J.M. Pawelek, *Punctate LC3B expression is a common feature of solid tumors and associated with proliferation, metastasis, and poor outcome.* Clin Cancer Res, 2012. **18**(2): p. 370-9.

37. Giatromanolaki, A., E. Sivridis, S. Mendrinos, A.V. Koutsopoulos, and M.I. Koukourakis, *Autophagy proteins in prostate cancer: relation with anaerobic metabolism and Gleason score.* Urol Oncol, 2014. **32**(1): p. 39 e11-8.
38. Zhao, H., M. Yang, J. Zhao, J. Wang, Y. Zhang, and Q. Zhang, *High expression of LC3B is associated with progression and poor outcome in triple-negative breast cancer.* Med Oncol, 2013. **30**(1): p. 475.
39. Mowers, E.E., M.N. Sharifi, and K.F. Macleod, *Autophagy in cancer metastasis.* Oncogene, 2016.
40. Sharifi, M.N., E.E. Mowers, L.E. Drake, C. Collier, H. Chen, M. Zamora, S. Mui, and K.F. Macleod, *Autophagy Promotes Focal Adhesion Disassembly and Cell Motility of Metastatic Tumor Cells through the Direct Interaction of Paxillin with LC3.* Cell Rep, 2016. **15**(8): p. 1660-72.
41. Lock, R., C.M. Kenific, A.M. Leidal, E. Salas, and J. Debnath, *Autophagy-dependent production of secreted factors facilitates oncogenic RAS-driven invasion.* Cancer Discov, 2014. **4**(4): p. 466-79.
42. Keulers, T.G., M.B. Schaaf, and K.M. Rouschop, *Autophagy-Dependent Secretion: Contribution to Tumor Progression.* Front Oncol, 2016. **6**: p. 251.
43. Peng, Y.F., Y.H. Shi, Y.H. Shen, Z.B. Ding, A.W. Ke, J. Zhou, S.J. Qiu, and J. Fan, *Promoting colonization in metastatic HCC cells by modulation of autophagy.* PLoS One, 2013. **8**(9): p. e74407.
44. Fung, C., R. Lock, S. Gao, E. Salas, and J. Debnath, *Induction of autophagy during extracellular matrix detachment promotes cell survival.* Mol Biol Cell, 2008. **19**(3): p. 797-806.
45. Gugnoni, M., V. Sancisi, G. Manzotti, G. Gandolfi, and A. Ciarrocchi, *Autophagy and epithelial-mesenchymal transition: an intricate interplay in cancer.* Cell Death Dis, 2016. **7**(12): p. e2520.
46. Sui, X., R. Chen, Z. Wang, Z. Huang, N. Kong, M. Zhang, W. Han, F. Lou, J. Yang, Q. Zhang, X. Wang, C. He, and H. Pan, *Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment.* Cell Death Dis, 2013. **4**: p. e838.
47. Knizhnik, A.V., W.P. Roos, T. Nikolova, S. Quiros, K.H. Tomaszowski, M. Christmann, and B. Kaina, *Survival and death strategies in glioma cells: autophagy, senescence and apoptosis triggered by a single type of temozolomide-induced DNA damage.* PLoS One, 2013. **8**(1): p. e55665.
48. Amaravadi, R.K., D. Yu, J.J. Lum, T. Bui, M.A. Christophorou, G.I. Evan, A. Thomas-Tikhonenko, and C.B. Thompson, *Autophagy inhibition enhances therapy-induced apoptosis in a Myc-induced model of lymphoma.* J Clin Invest, 2007. **117**(2): p. 326-36.
49. Guo, W., Y. Wang, Z. Wang, Y.P. Wang, and H. Zheng, *Inhibiting autophagy increases epirubicin's cytotoxicity in breast cancer cells.* Cancer Sci, 2016. **107**(11): p. 1610-1621.
50. Bellodi, C., M.R. Lidonnici, A. Hamilton, G.V. Helgason, A.R. Soliera, M. Ronchetti, S. Galavotti, K.W. Young, T. Selmi, R. Yacobi, R.A. Van Etten, N. Donato, A. Hunter, D. Dinsdale, E. Tirro, P. Vigneri, P. Nicotera, M.J. Dyer, T. Holyoake, P. Salomoni, and B. Calabretta, *Targeting autophagy potentiates tyrosine kinase inhibitor-induced cell death in Philadelphia chromosome-positive cells, including primary CML stem cells.* J Clin Invest, 2009. **119**(5): p. 1109-23.
51. Selvakumaran, M., R.K. Amaravadi, I.A. Vasilevskaya, and P.J. O'Dwyer, *Autophagy inhibition sensitizes colon cancer cells to antiangiogenic and cytotoxic therapy.* Clin Cancer Res, 2013. **19**(11): p. 2995-3007.
52. Chen, Y., X. Li, L. Guo, X. Wu, C. He, S. Zhang, Y. Xiao, Y. Yang, and D. Hao, *Combining radiation with autophagy inhibition enhances suppression of tumor growth and angiogenesis in esophageal cancer.* Mol Med Rep, 2015. **12**(2): p. 1645-52.
53. Onorati, A.V., M. Dyczynski, R. Ojha, and R.K. Amaravadi, *Targeting autophagy in cancer.* Cancer, 2018. **124**(16): p. 3307-3318.

54. Maes, H., A. Kuchnio, A. Peric, S. Moens, K. Nys, K. De Bock, A. Quaegebeur, S. Schoors, M. Georgiadou, J. Wouters, S. Vinckier, H. Vankelecom, M. Garmyn, A.C. Vion, F. Radtke, C. Boulanger, H. Gerhardt, E. Dejana, M. Dewerchin, B. Ghesquiere, W. Annaert, P. Agostinis, and P. Carmeliet, *Tumor vessel normalization by chloroquine independent of autophagy.* Cancer Cell, 2014. **26**(2): p. 190-206.
55. Maycotte, P., S. Aryal, C.T. Cummings, J. Thorburn, M.J. Morgan, and A. Thorburn, *Chloroquine sensitizes breast cancer cells to chemotherapy independent of autophagy.* Autophagy, 2012. **8**(2): p. 200-12.
56. Mauthe, M., I. Orhon, C. Rocchi, X. Zhou, M. Luhr, K.J. Hijlkema, R.P. Coppes, N. Engedal, M. Mari, and F. Reggiori, *Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion.* Autophagy, 2018. **14**(8): p. 1435-1455.
57. Pellegrini, P., A. Strambi, C. Zipoli, M. Hagg-Olofsson, M. Buoncervello, S. Linder, and A. De Milito, *Acidic extracellular pH neutralizes the autophagy-inhibiting activity of chloroquine: implications for cancer therapies.* Autophagy, 2014. **10**(4): p. 562-71.
58. Chen, Y., E. McMillan-Ward, J. Kong, S.J. Israels, and S.B. Gibson, *Mitochondrial electron-transport-chain inhibitors of complexes I and II induce autophagic cell death mediated by reactive oxygen species.* J Cell Sci, 2007. **120**(Pt 23): p. 4155-66.
59. Zhao, B., L. Qiang, J. Joseph, B. Kalyanaraman, B. Viollet, and Y.Y. He, *Mitochondrial dysfunction activates the AMPK signaling and autophagy to promote cell survival.* Genes Dis, 2016. **3**(1): p. 82-87.
60. Settembre, C., R. De Cegli, G. Mansueto, P.K. Saha, F. Vetrini, O. Visvikis, T. Huynh, A. Carissimo, D. Palmer, T.J. Klisch, A.C. Wollenberg, D. Di Bernardo, L. Chan, J.E. Irazoqui, and A. Ballabio, *TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop.* Nat Cell Biol, 2013. **15**(6): p. 647-58.
61. Fernandez-Mosquera, L., C.V. Diogo, K.F. Yambire, G.L. Santos, M. Luna Sanchez, P. Benit, P. Rustin, L.C. Lopez, I. Milosevic, and N. Raimundo, *Acute and chronic mitochondrial respiratory chain deficiency differentially regulate lysosomal biogenesis.* Sci Rep, 2017. **7**: p. 45076.
62. Graef, M. and J. Nunnari, *Mitochondria regulate autophagy by conserved signalling pathways.* EMBO J, 2011. **30**(11): p. 2101-14.
63. Thomas, H.E., Y. Zhang, J.A. Stefely, S.R. Veiga, G. Thomas, S.C. Kozma, and C.A. Mercer, *Mitochondrial Complex I Activity Is Required for Maximal Autophagy.* Cell Rep, 2018. **24**(9): p. 2404-2417 e8.
64. Duran, R.V., E.D. MacKenzie, H. Boulahbel, C. Frezza, L. Heiserich, S. Tardito, O. Bussolati, S. Rocha, M.N. Hall, and E. Gottlieb, *HIF-independent role of prolyl hydroxylases in the cellular response to amino acids.* Oncogene, 2013. **32**(38): p. 4549-56.
65. Duran, R.V., W. Oppliger, A.M. Robitaille, L. Heiserich, R. Skendaj, E. Gottlieb, and M.N. Hall, *Glutaminolysis activates Rag-mTORC1 signaling.* Mol Cell, 2012. **47**(3): p. 349-58.
66. Lorin, S., M.J. Tol, C. Bauvy, A. Strijland, C. Pous, A.J. Verhoeven, P. Codogno, and A.J. Meijer, *Glutamate dehydrogenase contributes to leucine sensing in the regulation of autophagy.* Autophagy, 2013. **9**(6): p. 850-60.
67. Villar, V.H., T.L. Nguyen, V. Delcroix, S. Teres, M. Bouchecareilh, B. Salin, C. Bodineau, P. Vacher, M. Priault, P. Soubeyran, and R.V. Duran, *mTORC1 inhibition in cancer cells protects from glutaminolysis-mediated apoptosis during nutrient limitation.* Nat Commun, 2017. **8**: p. 14124.
68. Eng, C.H., K. Yu, J. Lucas, E. White, and R.T. Abraham, *Ammonia derived from glutaminolysis is a diffusible regulator of autophagy.* Sci. Signal, 2010. **3**(119): p. ra31.
69. Harder, L.M., J. Bunkenborg, and J.S. Andersen, *Inducing autophagy: a comparative phosphoproteomic study of the cellular response to ammonia and rapamycin.* Autophagy, 2014. **10**(2): p. 339-55.
70. Marino, G. and G. Kroemer, *Ammonia: a diffusible factor released by proliferating cells that induces autophagy.* Sci Signal, 2010. **3**(124): p. pe19.

71. Ko, Y.H., Z. Lin, N. Flomenberg, R.G. Pestell, A. Howell, F. Sotgia, M.P. Lisanti, and U.E. Martinez-Outschoorn, *Glutamine fuels a vicious cycle of autophagy in the tumor stroma and oxidative mitochondrial metabolism in epithelial cancer cells: implications for preventing chemotherapy resistance.* Cancer Biol Ther, 2011. **12**(12): p. 1085-97.
72. Whitaker-Menezes, D., U.E. Martinez-Outschoorn, Z. Lin, A. Ertel, N. Flomenberg, A.K. Witkiewicz, R.C. Birbe, A. Howell, S. Pavlides, R. Gandara, R.G. Pestell, F. Sotgia, N.J. Philp, and M.P. Lisanti, *Evidence for a stromal-epithelial "lactate shuttle" in human tumors: MCT4 is a marker of oxidative stress in cancer-associated fibroblasts.* Cell Cycle, 2011. **10**(11): p. 1772-83.
73. Chen, Y.J., N.G. Mahieu, X. Huang, M. Singh, P.A. Crawford, S.L. Johnson, R.W. Gross, J. Schaefer, and G.J. Patti, *Lactate metabolism is associated with mammalian mitochondria.* Nat Chem Biol, 2016. **12**(11): p. 937-943.
74. Corbet, C. and O. Feron, *Emerging roles of lipid metabolism in cancer progression.* Curr Opin Clin Nutr Metab Care, 2017. **20**(4): p. 254-260.
75. Schlaepfer, I.R., L. Rider, L.U. Rodrigues, M.A. Gijon, C.T. Pac, L. Romero, A. Cimic, S.J. Sirintrapun, L.M. Glode, R.H. Eckel, and S.D. Cramer, *Lipid catabolism via CPT1 as a therapeutic target for prostate cancer.* Mol Cancer Ther, 2014. **13**(10): p. 2361-71.
76. Wen, Y.A., X. Xing, J.W. Harris, Y.Y. Zaytseva, M.I. Mitov, D.L. Napier, H.L. Weiss, B. Mark Evers, and T. Gao, *Adipocytes activate mitochondrial fatty acid oxidation and autophagy to promote tumor growth in colon cancer.* Cell Death Dis, 2017. **8**(2): p. e2593.
77. Tabe, Y., S. Yamamoto, K. Saitoh, K. Sekihara, N. Monma, K. Ikeo, K. Mogushi, M. Shikami, V. Ruvolo, J. Ishizawa, N. Hail, Jr., S. Kazuno, M. Igarashi, H. Matsushita, Y. Yamanaka, H. Arai, I. Nagaoka, T. Miida, Y. Hayashizaki, M. Konopleva, and M. Andreeff, *Bone Marrow Adipocytes Facilitate Fatty Acid Oxidation Activating AMPK and a Transcriptional Network Supporting Survival of Acute Monocytic Leukemia Cells.* Cancer Res, 2017. **77**(6): p. 1453-1464.
78. Rambold, A.S., S. Cohen, and J. Lippincott-Schwartz, *Fatty acid trafficking in starved cells: regulation by lipid droplet lipolysis, autophagy, and mitochondrial fusion dynamics.* Dev Cell, 2015. **32**(6): p. 678-92.
79. Alexander, A., S.L. Cai, J. Kim, A. Nanez, M. Sahin, K.H. MacLean, K. Inoki, K.L. Guan, J. Shen, M.D. Person, D. Kusewitt, G.B. Mills, M.B. Kastan, and C.L. Walker, *ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS.* Proc Natl Acad Sci U S A, 2010. **107**(9): p. 4153-8.
80. Song, C., S.K. Mitter, X. Qi, E. Beli, H.V. Rao, J. Ding, C.S. Ip, H. Gu, D. Akin, W.A. Dunn, Jr., C. Bowes Rickman, A.S. Lewin, M.B. Grant, and M.E. Boulton, *Oxidative stress-mediated NFkappaB phosphorylation upregulates p62/SQSTM1 and promotes retinal pigmented epithelial cell survival through increased autophagy.* PLoS One, 2017. **12**(2): p. e0171940.
81. Scherz-Shouval, R., E. Shvets, E. Fass, H. Shorer, L. Gil, and Z. Elazar, *Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4.* EMBO J, 2007. **26**(7): p. 1749-60.
82. Zhang, X., X. Cheng, L. Yu, J. Yang, R. Calvo, S. Patnaik, X. Hu, Q. Gao, M. Yang, M. Lawas, M. Delling, J. Marugan, M. Ferrer, and H. Xu, *MCOLN1 is a ROS sensor in lysosomes that regulates autophagy.* Nat Commun, 2016. **7**: p. 12109.
83. Wang, Q., L. Huang, and J. Yue, *Oxidative stress activates the TRPM2-Ca(2+)-CaMKII-ROS signaling loop to induce cell death in cancer cells.* Biochim Biophys Acta Mol Cell Res, 2017. **1864**(6): p. 957-967.
84. Chen, Y., M.B. Azad, and S.B. Gibson, *Superoxide is the major reactive oxygen species regulating autophagy.* Cell Death. Differ, 2009. **16**(7): p. 1040-1052.
85. Li, A.E., H. Ito, Rovira, II, K.S. Kim, K. Takeda, Z.Y. Yu, V.J. Ferrans, and T. Finkel, *A role for reactive oxygen species in endothelial cell anoikis.* Circ Res, 1999. **85**(4): p. 304-10.
86. Schafer, Z.T., A.R. Grassian, L. Song, Z. Jiang, Z. Gerhart-Hines, H.Y. Irie, S. Gao, P. Puigserver, and J.S. Brugge, *Antioxidant and oncogene rescue of metabolic defects caused by loss of matrix attachment.* Nature, 2009. **461**(7260): p. 109-13.

87. Avivar-Valderas, A., E. Salas, E. Bobrovnikova-Marjon, J.A. Diehl, C. Nagi, J. Debnath, and J.A. Aguirre-Ghiso, *PERK integrates autophagy and oxidative stress responses to promote survival during extracellular matrix detachment.* Mol Cell Biol, 2011. **31**(17): p. 3616-29.
88. Ozben, T., *Oxidative stress and apoptosis: impact on cancer therapy.* J Pharm Sci, 2007. **96**(9): p. 2181-96.
89. Amantini, C., M.B. Morelli, M. Nabissi, C. Cardinali, M. Santoni, A. Gismondi, and G. Santoni, *Capsaicin triggers autophagic cell survival which drives epithelial mesenchymal transition and chemoresistance in bladder cancer cells in an Hedgehog-dependent manner.* Oncotarget, 2016. **7**(31): p. 50180-50194.
90. Chen, N., L. Wu, H. Yuan, and J. Wang, *ROS/Autophagy/Nrf2 Pathway Mediated Low-Dose Radiation Induced Radio-Resistance in Human Lung Adenocarcinoma A549 Cell.* Int J Biol Sci, 2015. **11**(7): p. 833-44.
91. Naon, D. and L. Scorrano, *At the right distance: ER-mitochondria juxtaposition in cell life and death.* Biochim Biophys Acta, 2014. **1843**(10): p. 2184-94.
92. Hailey, D.W., A.S. Rambold, P. Satpute-Krishnan, K. Mitra, R. Sougrat, P.K. Kim, and J. Lippincott-Schwartz, *Mitochondria supply membranes for autophagosome biogenesis during starvation.* Cell, 2010. **141**(4): p. 656-67.
93. Kabeya, Y., N. Mizushima, A. Yamamoto, S. Oshitani-Okamoto, Y. Ohsumi, and T. Yoshimori, *LC3, GABARAP and GATE16 localize to autophagosomal membrane depending on form-II formation.* J Cell Sci, 2004. **117**(Pt 13): p. 2805-12.
94. Cardenas, C., R.A. Miller, I. Smith, T. Bui, J. Molgo, M. Muller, H. Vais, K.H. Cheung, J. Yang, I. Parker, C.B. Thompson, M.J. Birnbaum, K.R. Hallows, and J.K. Foskett, *Essential regulation of cell bioenergetics by constitutive InsP3 receptor Ca2+ transfer to mitochondria.* Cell, 2010. **142**(2): p. 270-83.
95. Bidaux, G., D. Gordienko, G. Shapovalov, V. Farfariello, A.S. Borowiec, O. Iamshanova, L. Lemonnier, M. Gueguinou, R. Guibon, G. Fromont, M. Paillard, Y. Gouriou, C. Chouabe, E. Dewailly, D. Gkika, P. Lopez-Alvarado, J. Carlos Menendez, L. Heliot, C. Slomianny, and N. Prevarskaya, *4TM-TRPM8 channels are new gatekeepers of the ER-mitochondria Ca(2+) transfer.* Biochim Biophys Acta Mol Cell Res, 2018. **1865**(7): p. 981-994.
96. O'Rourke, B., *Mitochondrial ion channels.* Annu Rev Physiol, 2007. **69**: p. 19-49.
97. Szabo, I. and M. Zoratti, *Mitochondrial channels: ion fluxes and more.* Physiol Rev, 2014. **94**(2): p. 519-608.
98. Cardenas, C., M. Muller, A. McNeal, A. Lovy, F. Jana, G. Bustos, F. Urra, N. Smith, J. Molgo, J.A. Diehl, T.W. Ridky, and J.K. Foskett, *Selective Vulnerability of Cancer Cells by Inhibition of Ca(2+) Transfer from Endoplasmic Reticulum to Mitochondria.* Cell Rep, 2016. **14**(10): p. 2313-24.
99. Gomez-Suaga, P., S. Paillusson, R. Stoica, W. Noble, D.P. Hanger, and C.C.J. Miller, *The ER-Mitochondria Tethering Complex VAPB-PTPIP51 Regulates Autophagy.* Curr Biol, 2017. **27**(3): p. 371-385.
100. Herrera-Cruz, M.S. and T. Simmen, *Cancer: Untethering Mitochondria from the Endoplasmic Reticulum?* Front Oncol, 2017. **7**: p. 105.
101. Jin, S.M., M. Lazarou, C. Wang, L.A. Kane, D.P. Narendra, and R.J. Youle, *Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL.* J Cell Biol, 2010. **191**(5): p. 933-42.
102. Narendra, D.P., S.M. Jin, A. Tanaka, D.F. Suen, C.A. Gautier, J. Shen, M.R. Cookson, and R.J. Youle, *PINK1 is selectively stabilized on impaired mitochondria to activate Parkin.* PLoS Biol, 2010. **8**(1): p. e1000298.
103. Sarraf, S.A., M. Raman, V. Guarani-Pereira, M.E. Sowa, E.L. Huttlin, S.P. Gygi, and J.W. Harper, *Landscape of the PARKIN-dependent ubiquitylome in response to mitochondrial depolarization.* Nature, 2013. **496**(7445): p. 372-6.

104. Geisler, S., K.M. Holmstrom, D. Skujat, F.C. Fiesel, O.C. Rothfuss, P.J. Kahle, and W. Springer, *PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1.* Nat Cell Biol, 2010. **12**(2): p. 119-31.
105. Lee, J.Y., Y. Nagano, J.P. Taylor, K.L. Lim, and T.P. Yao, *Disease-causing mutations in parkin impair mitochondrial ubiquitination, aggregation, and HDAC6-dependent mitophagy.* J Cell Biol, 2010. **189**(4): p. 671-9.
106. Hollville, E., R.G. Carroll, S.P. Cullen, and S.J. Martin, *Bcl-2 family proteins participate in mitochondrial quality control by regulating Parkin/PINK1-dependent mitophagy.* Mol Cell, 2014. **55**(3): p. 451-66.
107. Lazarou, M., D.A. Sliter, L.A. Kane, S.A. Sarraf, C. Wang, J.L. Burman, D.P. Sideris, A.I. Fogel, and R.J. Youle, *The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy.* Nature, 2015. **524**(7565): p. 309-314.
108. Richter, B., D.A. Sliter, L. Herhaus, A. Stolz, C. Wang, P. Beli, G. Zaffagnini, P. Wild, S. Martens, S.A. Wagner, R.J. Youle, and I. Dikic, *Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria.* Proc Natl Acad Sci U S A, 2016. **113**(15): p. 4039-44.
109. Drake, L.E., M.Z. Springer, L.P. Poole, C.J. Kim, and K.F. Macleod, *Expanding perspectives on the significance of mitophagy in cancer.* Semin Cancer Biol, 2017. **47**: p. 110-124.
110. Bellot, G., R. Garcia-Medina, P. Gounon, J. Chiche, D. Roux, J. Pouyssegur, and N.M. Mazure, *Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains.* Mol Cell Biol, 2009. **29**(10): p. 2570-81.
111. Sowter, H.M., P.J. Ratcliffe, P. Watson, A.H. Greenberg, and A.L. Harris, *HIF-1-dependent regulation of hypoxic induction of the cell death factors BNIP3 and NIX in human tumors.* Cancer Res, 2001. **61**(18): p. 6669-73.
112. Liu, L., D. Feng, G. Chen, M. Chen, Q. Zheng, P. Song, Q. Ma, C. Zhu, R. Wang, W. Qi, L. Huang, P. Xue, B. Li, X. Wang, H. Jin, J. Wang, F. Yang, P. Liu, Y. Zhu, S. Sui, and Q. Chen, *Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells.* Nat Cell Biol, 2012. **14**(2): p. 177-85.
113. Melser, S., E.H. Chatelain, J. Lavie, W. Mahfouf, C. Jose, E. Obre, S. Goorden, M. Priault, Y. Elgersma, H.R. Rezvani, R. Rossignol, and G. Benard, *Rheb regulates mitophagy induced by mitochondrial energetic status.* Cell Metab, 2013. **17**(5): p. 719-30.
114. Ivankovic, D., K.Y. Chau, A.H. Schapira, and M.E. Gegg, *Mitochondrial and lysosomal biogenesis are activated following PINK1/parkin-mediated mitophagy.* J Neurochem, 2016. **136**(2): p. 388-402.
115. Chu, C.T., J. Ji, R.K. Dagda, J.F. Jiang, Y.Y. Tyurina, A.A. Kapralov, V.A. Tyurin, N. Yanamala, I.H. Shrivastava, D. Mohammadyani, K.Z.Q. Wang, J. Zhu, J. Klein-Seetharaman, K. Balasubramanian, A.A. Amoscato, G. Borisenko, Z. Huang, A.M. Gusdon, A. Cheikhi, E.K. Steer, R. Wang, C. Baty, S. Watkins, I. Bahar, H. Bayir, and V.E. Kagan, *Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells.* Nat Cell Biol, 2013. **15**(10): p. 1197-1205.
116. Kagan, V.E., J. Jiang, Z. Huang, Y.Y. Tyurina, C. Desbourdes, C. Cottet-Rousselle, H.H. Dar, M. Verma, V.A. Tyurin, A.A. Kapralov, A. Cheikhi, G. Mao, D. Stolz, C.M. St Croix, S. Watkins, Z. Shen, Y. Li, M.L. Greenberg, M. Tokarska-Schlattner, M. Boissan, M.L. Lacombe, R.M. Epand, C.T. Chu, R.K. Mallampalli, H. Bayir, and U. Schlattner, *NDPK-D (NM23-H4)-mediated externalization of cardiolipin enables elimination of depolarized mitochondria by mitophagy.* Cell Death Differ, 2016. **23**(7): p. 1140-51.
117. Lee, Y., H.Y. Lee, R.A. Hanna, and A.B. Gustafsson, *Mitochondrial autophagy by Bnip3 involves Drp1-mediated mitochondrial fission and recruitment of Parkin in cardiac myocytes.* Am J Physiol Heart Circ Physiol, 2011. **301**(5): p. H1924-31.
118. Buhlman, L., M. Damiano, G. Bertolin, R. Ferrando-Miguel, A. Lombes, A. Brice, and O. Corti, *Functional interplay between Parkin and Drp1 in mitochondrial fission and clearance.* Biochim Biophys Acta, 2014. **1843**(9): p. 2012-26.

119. Wu, W., C. Lin, K. Wu, L. Jiang, X. Wang, W. Li, H. Zhuang, X. Zhang, H. Chen, S. Li, Y. Yang, Y. Lu, J. Wang, R. Zhu, L. Zhang, S. Sui, N. Tan, B. Zhao, J. Zhang, L. Li, and D. Feng, *FUNDC1 regulates mitochondrial dynamics at the ER-mitochondrial contact site under hypoxic conditions.* EMBO J, 2016. **35**(13): p. 1368-84.
120. Gelmetti, V., P. De Rosa, L. Torosantucci, E.S. Marini, A. Romagnoli, M. Di Rienzo, G. Arena, D. Vignone, G.M. Fimia, and E.M. Valente, *PINK1 and BECN1 relocalize at mitochondria-associated membranes during mitophagy and promote ER-mitochondria tethering and autophagosome formation.* Autophagy, 2017. **13**(4): p. 654-669.
121. Fujiwara, M., H. Marusawa, H.Q. Wang, A. Iwai, K. Ikeuchi, Y. Imai, A. Kataoka, N. Nukina, R. Takahashi, and T. Chiba, *Parkin as a tumor suppressor gene for hepatocellular carcinoma.* Oncogene, 2008. **27**(46): p. 6002-11.
122. Li, C., Y. Zhang, X. Cheng, H. Yuan, S. Zhu, J. Liu, Q. Wen, Y. Xie, J. Liu, G. Kroemer, D.J. Klionsky, M.T. Lotze, H.J. Zeh, R. Kang, and D. Tang, *PINK1 and PARK2 Suppress Pancreatic Tumorigenesis through Control of Mitochondrial Iron-Mediated Immunometabolism.* Dev Cell, 2018. **46**(4): p. 441-455 e8.
123. Poulogiannis, G., R.E. McIntyre, M. Dimitriadi, J.R. Apps, C.H. Wilson, K. Ichimura, F. Luo, L.C. Cantley, A.H. Wyllie, D.J. Adams, and M.J. Arends, *PARK2 deletions occur frequently in sporadic colorectal cancer and accelerate adenoma development in Apc mutant mice.* Proc Natl Acad Sci U S A, 2010. **107**(34): p. 15145-50.
124. Veeriah, S., B.S. Taylor, S. Meng, F. Fang, E. Yilmaz, I. Vivanco, M. Janakiraman, N. Schultz, A.J. Hanrahan, W. Pao, M. Ladanyi, C. Sander, A. Heguy, E.C. Holland, P.B. Paty, P.S. Mischel, L. Liau, T.F. Cloughesy, I.K. Mellinghoff, D.B. Solit, and T.A. Chan, *Somatic mutations of the Parkinson's disease-associated gene PARK2 in glioblastoma and other human malignancies.* Nat Genet, 2010. **42**(1): p. 77-82.
125. Hu, H.H., C. Kannengiesser, S. Lesage, J. Andre, S. Mourah, L. Michel, V. Descamps, N. Basset-Seguin, M. Bagot, A. Bensussan, C. Lebbe, L. Deschamps, P. Saiag, M.T. Leccia, B. Bressac-de-Paillerets, A. Tsalamlal, R. Kumar, S. Klebe, B. Grandchamp, N. Andrieu-Abadie, L. Thomas, A. Brice, N. Dumaz, and N. Soufir, *PARKIN Inactivation Links Parkinson's Disease to Melanoma.* J Natl Cancer Inst, 2016. **108**(3).
126. Lee, S., J. She, B. Deng, J. Kim, M. de Andrade, J. Na, Z. Sun, J.A. Wampfler, J.M. Cunningham, Y. Wu, A.H. Limper, M.C. Aubry, C. Wendt, P. Biterman, P. Yang, and Z. Lou, *Multiple-level validation identifies PARK2 in the development of lung cancer and chronic obstructive pulmonary disease.* Oncotarget, 2016. **7**(28): p. 44211-44223.
127. Letessier, A., S. Garrido-Urbani, C. Ginestier, G. Fournier, B. Esterni, F. Monville, J. Adelaide, J. Geneix, L. Xerri, P. Dubreuil, P. Viens, E. Charafe-Jauffret, J. Jacquemier, D. Birnbaum, M. Lopez, and M. Chaffanet, *Correlated break at PARK2/FRA6E and loss of AF-6/Afadin protein expression are associated with poor outcome in breast cancer.* Oncogene, 2007. **26**(2): p. 298-307.
128. Cesari, R., E.S. Martin, G.A. Calin, F. Pentimalli, R. Bichi, H. McAdams, F. Trapasso, A. Drusco, M. Shimizu, V. Masciullo, G. D'Andrilli, G. Scambia, M.C. Picchio, H. Alder, A.K. Godwin, and C.M. Croce, *Parkin, a gene implicated in autosomal recessive juvenile parkinsonism, is a candidate tumor suppressor gene on chromosome 6q25-q27.* Proc Natl Acad Sci U S A, 2003. **100**(10): p. 5956-61.
129. Zhang, C., M. Lin, R. Wu, X. Wang, B. Yang, A.J. Levine, W. Hu, and Z. Feng, *Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect.* Proc Natl Acad Sci U S A, 2011. **108**(39): p. 16259-64.
130. Liu, J., C. Zhang, Y. Zhao, X. Yue, H. Wu, S. Huang, J. Chen, K. Tomsky, H. Xie, C.A. Khella, M.L. Gatza, D. Xia, J. Gao, E. White, B.G. Haffty, W. Hu, and Z. Feng, *Parkin targets HIF-1alpha for ubiquitination and degradation to inhibit breast tumor progression.* Nat Commun, 2017. **8**(1): p. 1823.
131. Akada, M., T. Crnogorac-Jurcevic, S. Lattimore, P. Mahon, R. Lopes, M. Sunamura, S. Matsuno, and N.R. Lemoine, *Intrinsic chemoresistance to gemcitabine is associated with*

decreased expression of BNIP3 in pancreatic cancer. Clin Cancer Res, 2005. **11**(8): p. 3094-101.
132. Erkan, M., J. Kleeff, I. Esposito, T. Giese, K. Ketterer, M.W. Buchler, N.A. Giese, and H. Friess, *Loss of BNIP3 expression is a late event in pancreatic cancer contributing to chemoresistance and worsened prognosis.* Oncogene, 2005. **24**(27): p. 4421-32.
133. Chourasia, A.H., K. Tracy, C. Frankenberger, M.L. Boland, M.N. Sharifi, L.E. Drake, J.R. Sachleben, J.M. Asara, J.W. Locasale, G.S. Karczmar, and K.F. Macleod, *Mitophagy defects arising from BNip3 loss promote mammary tumor progression to metastasis.* EMBO Rep, 2015. **16**(9): p. 1145-63.
134. Li, W., Y. Li, S. Siraj, H. Jin, Y. Fan, X. Yang, X. Huang, X. Wang, J. Wang, L. Liu, L. Du, and Q. Chen, *FUN14 Domain-Containing 1-Mediated Mitophagy Suppresses Hepatocarcinogenesis by Inhibition of Inflammasome Activation in Mice.* Hepatology, 2018.
135. Vara-Perez, M., H. Maes, S. Van Dingenen, and P. Agostinis, *BNIP3 contributes to the glutamine-driven aggressive behavior of melanoma cells.* Biol Chem, 2018.
136. Hui, L., H. Wu, T.W. Wang, N. Yang, X. Guo, and X.J. Jang, *Hydrogen peroxide-induced mitophagy contributes to laryngeal cancer cells survival via the upregulation of FUNDC1.* Clin Transl Oncol, 2018.
137. Lee, Y.S., Y.Y. Jung, M.H. Park, I.J. Yeo, H.S. Im, K.T. Nam, H.D. Kim, S.K. Kang, J.K. Song, Y.R. Kim, D.Y. Choi, P.H. Park, S.B. Han, J.S. Yun, and J.T. Hong, *Deficiency of parkin suppresses melanoma tumor development and metastasis through inhibition of MFN2 ubiquitination.* Cancer Lett, 2018. **433**: p. 156-164.
138. Villa, E., E. Proics, C. Rubio-Patino, S. Obba, B. Zunino, J.P. Bossowski, R.M. Rozier, J. Chiche, L. Mondragon, J.S. Riley, S. Marchetti, E. Verhoeyen, S.W.G. Tait, and J.E. Ricci, *Parkin-Independent Mitophagy Controls Chemotherapeutic Response in Cancer Cells.* Cell Rep, 2017. **20**(12): p. 2846-2859.
139. Maes, H., S. Van Eygen, D.V. Krysko, P. Vandenabeele, K. Nys, K. Rillaerts, A.D. Garg, T. Verfaillie, and P. Agostinis, *BNIP3 supports melanoma cell migration and vasculogenic mimicry by orchestrating the actin cytoskeleton.* Cell Death Dis, 2014. **5**: p. e1127.
140. Sun, L., T. Li, Q. Wei, Y. Zhang, X. Jia, Z. Wan, and L. Han, *Upregulation of BNIP3 mediated by ERK/HIF-1alpha pathway induces autophagy and contributes to anoikis resistance of hepatocellular carcinoma cells.* Future Oncol, 2014. **10**(8): p. 1387-98.
141. Wu, H., S. Huang, Z. Chen, W. Liu, X. Zhou, and D. Zhang, *Hypoxia-induced autophagy contributes to the invasion of salivary adenoid cystic carcinoma through the HIF-1alpha/BNIP3 signaling pathway.* Mol Med Rep, 2015. **12**(5): p. 6467-74.
142. Yan, C., L. Luo, C.Y. Guo, S. Goto, Y. Urata, J.H. Shao, and T.S. Li, *Doxorubicin-induced mitophagy contributes to drug resistance in cancer stem cells from HCT8 human colorectal cancer cells.* Cancer Lett, 2017. **388**: p. 34-42.
143. Hou, H., P. Er, J. Cheng, X. Chen, X. Ding, Y. Wang, X. Chen, Z. Yuan, Q. Pang, P. Wang, and D. Qian, *High expression of FUNDC1 predicts poor prognostic outcomes and is a promising target to improve chemoradiotherapy effects in patients with cervical cancer.* Cancer Med, 2017. **6**(8): p. 1871-1881.
144. Koop, E.A., T. van Laar, D.F. van Wichen, R.A. de Weger, E. Wall, and P.J. van Diest, *Expression of BNIP3 in invasive breast cancer: correlations with the hypoxic response and clinicopathological features.* BMC Cancer, 2009. **9**: p. 175.
145. Sowter, H.M., M. Ferguson, C. Pym, P. Watson, S.B. Fox, C. Han, and A.L. Harris, *Expression of the cell death genes BNip3 and NIX in ductal carcinoma in situ of the breast; correlation of BNip3 levels with necrosis and grade.* J Pathol, 2003. **201**(4): p. 573-80.
146. Jiang, Z., F. Yu, and M. Li, *Upregulation of BCL2 19 kD Protein-Interacting Protein 3 (BNIP3) is Predictive of Unfavorable Prognosis in Uveal Melanoma.* Med Sci Monit, 2018. **24**: p. 4711-4717.

147. Gang, H., R. Dhingra, J. Lin, Y. Hai, Y. Aviv, V. Margulets, M. Hamedani, T. Thanasupawat, E. Leygue, T. Klonisch, J.R. Davie, and L.A. Kirshenbaum, *PDK2-mediated alternative splicing switches Bnip3 from cell death to cell survival.* J Cell Biol, 2015. **210**(7): p. 1101-15.
148. Gazzano, E., L. Lazzarato, B. Rolando, J. Kopecka, S. Guglielmo, C. Costamagna, K. Chegaev, and C. Riganti, *Mitochondrial Delivery of Phenol Substructure Triggers Mitochondrial Depolarization and Apoptosis of Cancer Cells.* Front Pharmacol, 2018. **9**: p. 580.
149. Biel, T.G. and V.A. Rao, *Mitochondrial dysfunction activates lysosomal-dependent mitophagy selectively in cancer cells.* Oncotarget, 2018. **9**(1): p. 995-1011.
150. Feng, S., H. Li, Y. Tai, J. Huang, Y. Su, J. Abramowitz, M.X. Zhu, L. Birnbaumer, and Y. Wang, *Canonical transient receptor potential 3 channels regulate mitochondrial calcium uptake.* Proc Natl Acad Sci U S A, 2013. **110**(27): p. 11011-6.
151. Miller, B.A., N.E. Hoffman, S. Merali, X.Q. Zhang, J. Wang, S. Rajan, S. Shanmughapriya, E. Gao, C.A. Barrero, K. Mallilankaraman, J. Song, T. Gu, I. Hirschler-Laszkiewicz, W.J. Koch, A.M. Feldman, M. Madesh, and J.Y. Cheung, *TRPM2 channels protect against cardiac ischemia-reperfusion injury: role of mitochondria.* J Biol Chem, 2014. **289**(11): p. 7615-29.
152. Griffiths, E.J. and G.A. Rutter, *Mitochondrial calcium as a key regulator of mitochondrial ATP production in mammalian cells.* Biochim Biophys Acta, 2009. **1787**(11): p. 1324-33.
153. Laskowski, M., B. Augustynek, B. Kulawiak, P. Koprowski, P. Bednarczyk, W. Jarmuszkiewicz, and A. Szewczyk, *What do we not know about mitochondrial potassium channels?* Biochim Biophys Acta, 2016. **1857**(8): p. 1247-1257.
154. Kane, M.S., A. Paris, P. Codron, J. Cassereau, V. Procaccio, G. Lenaers, P. Reynier, and A. Chevrollier, *Current mechanistic insights into the CCCP-induced cell survival response.* Biochem Pharmacol, 2018. **148**: p. 100-110.
155. Sun, Y., A.A. Vashisht, J. Tchieu, J.A. Wohlschlegel, and L. Dreier, *Voltage-dependent anion channels (VDACs) recruit Parkin to defective mitochondria to promote mitochondrial autophagy.* J Biol Chem, 2012. **287**(48): p. 40652-60.
156. MacVicar, T.D., L.V. Mannack, R.M. Lees, and J.D. Lane, *Targeted siRNA Screens Identify ER-to-Mitochondrial Calcium Exchange in Autophagy and Mitophagy Responses in RPE1 Cells.* Int J Mol Sci, 2015. **16**(6): p. 13356-80.
157. Mazure, N.M., *VDAC in cancer.* Biochim Biophys Acta Bioenerg, 2017. **1858**(8): p. 665-673.
158. Shoshan-Barmatz, V., Y. Krelin, A. Shteinfer-Kuzmine, and T. Arif, *Voltage-Dependent Anion Channel 1 As an Emerging Drug Target for Novel Anti-Cancer Therapeutics.* Front Oncol, 2017. **7**: p. 154.
159. Arif, T., L. Vasilkovsky, Y. Refaely, A. Konson, and V. Shoshan-Barmatz, *Silencing VDAC1 Expression by siRNA Inhibits Cancer Cell Proliferation and Tumor Growth In Vivo.* Mol Ther Nucleic Acids, 2014. **3**: p. e159.
160. Vultur, A., C.S. Gibhardt, H. Stanisz, and I. Bogeski, *The role of the mitochondrial calcium uniporter (MCU) complex in cancer.* Pflugers Arch, 2018. **470**(8): p. 1149-1163.
161. Tang, S., X. Wang, Q. Shen, X. Yang, C. Yu, C. Cai, G. Cai, X. Meng, and F. Zou, *Mitochondrial Ca(2)(+) uniporter is critical for store-operated Ca(2)(+) entry-dependent breast cancer cell migration.* Biochem Biophys Res Commun, 2015. **458**(1): p. 186-93.
162. Yu, C., Y. Wang, J. Peng, Q. Shen, M. Chen, W. Tang, X. Li, C. Cai, B. Wang, S. Cai, X. Meng, and F. Zou, *Mitochondrial calcium uniporter as a target of microRNA-340 and promoter of metastasis via enhancing the Warburg effect.* Oncotarget, 2017. **8**(48): p. 83831-83844.
163. Ren, T., H. Zhang, J. Wang, J. Zhu, M. Jin, Y. Wu, X. Guo, L. Ji, Q. Huang, H. Zhang, H. Yang, and J. Xing, *MCU-dependent mitochondrial Ca(2+) inhibits NAD(+)/SIRT3/SOD2 pathway to promote ROS production and metastasis of HCC cells.* Oncogene, 2017. **36**(42): p. 5897-5909.
164. Mallilankaraman, K., C. Cardenas, P.J. Doonan, H.C. Chandramoorthy, K.M. Irrinki, T. Golenar, G. Csordas, P. Madireddi, J. Yang, M. Muller, R. Miller, J.E. Kolesar, J. Molgo, B. Kaufman, G. Hajnoczky, J.K. Foskett, and M. Madesh, *MCUR1 is an essential component of mitochondrial Ca2+ uptake that regulates cellular metabolism.* Nat Cell Biol, 2012. **14**(12): p. 1336-43.

165. Tomar, D., Z. Dong, S. Shanmughapriya, D.A. Koch, T. Thomas, N.E. Hoffman, S.A. Timbalia, S.J. Goldman, S.L. Breves, D.P. Corbally, N. Nemani, J.P. Fairweather, A.R. Cutri, X. Zhang, J. Song, F. Jana, J. Huang, C. Barrero, J.E. Rabinowitz, T.S. Luongo, S.M. Schumacher, M.E. Rockman, A. Dietrich, S. Merali, J. Caplan, P. Stathopulos, R.S. Ahima, J.Y. Cheung, S.R. Houser, W.J. Koch, V. Patel, V.M. Gohil, J.W. Elrod, S. Rajan, and M. Madesh, *MCUR1 Is a Scaffold Factor for the MCU Complex Function and Promotes Mitochondrial Bioenergetics.* Cell Rep, 2016. **15**(8): p. 1673-85.
166. Ren, T., J. Wang, H. Zhang, P. Yuan, J. Zhu, Y. Wu, Q. Huang, X. Guo, J. Zhang, L. Ji, J. Li, H. Zhang, H. Yang, and J. Xing, *MCUR1-Mediated Mitochondrial Calcium Signaling Facilitates Cell Survival of Hepatocellular Carcinoma via Reactive Oxygen Species-Dependent P53 Degradation.* Antioxid Redox Signal, 2018. **28**(12): p. 1120-1136.
167. Chen, S.J., N.E. Hoffman, S. Shanmughapriya, L. Bao, K. Keefer, K. Conrad, S. Merali, Y. Takahashi, T. Abraham, I. Hirschler-Laszkiewicz, J. Wang, X.Q. Zhang, J. Song, C. Barrero, Y. Shi, Y.I. Kawasawa, M. Bayerl, T. Sun, M. Barbour, H.G. Wang, M. Madesh, J.Y. Cheung, and B.A. Miller, *A splice variant of the human ion channel TRPM2 modulates neuroblastoma tumor growth through hypoxia-inducible factor (HIF)-1/2alpha.* J Biol Chem, 2014. **289**(52): p. 36284-302.
168. Almasi, S., B.E. Kennedy, M. El-Aghil, A.M. Sterea, S. Gujar, S. Partida-Sanchez, and Y. El Hiani, *TRPM2 channel-mediated regulation of autophagy maintains mitochondrial function and promotes gastric cancer cell survival via the JNK-signaling pathway.* J Biol Chem, 2018. **293**(10): p. 3637-3650.
169. Koh, D.W., D.P. Powell, S.D. Blake, J.L. Hoffman, M.M. Hopkins, and X. Feng, *Enhanced cytotoxicity in triple-negative and estrogen receptorpositive breast adenocarcinoma cells due to inhibition of the transient receptor potential melastatin-2 channel.* Oncol Rep, 2015. **34**(3): p. 1589-98.