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Invited Review in Seminars in Cell & Developmental Biology

Special Issue: Mitochondrial metabolic alterations in cancer cells and related therapeutic targets

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Autophagy and mitophagy in cancer metabolic remodelling

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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

1 Introduction

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

20

21 1. Targeting mitochondrial metabolism and autophagy in cancer

22 1.1. Mitochondrial metabolism in tumours

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

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

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

47

48 1.2. Autophagy

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

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

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

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

101

102 1.3. Mitochondrial metabolism in regulation of autophagy

103 1.3.1. Energy metabolism

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

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

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

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

146 Another particular adaptation of cancer cells which depends on autophagy is the metabolic symbiosis
147 based on lactate exchanges between glycolytic, lactate-producing cells, and oxidative, lactate-
148 consuming cells. These lactate exchanges have been described between cancer cells from different
149 metabolic phenotypes [4] and between cancer cells and fibroblasts [72]. This cooperation requires
150 the entry of lactate into the oxidative cells, a process facilitated by the lactate-proton symporter
151 monocarboxylate transporter type 1 (MCT1), and its oxidation to pyruvate by lactate dehydrogenase
152 B (LDHB). In oxidative cancer cells, lactate is used for OXPHOS [4] and for the production of lipids
153 [73]. Interestingly the oxidation of lactate by LDHB also participates to lysosome function and
154 activates autophagy in cancer cells [28]. The activation of autophagy by lactate utilisation promotes
155 cancer cell survival and tumour growth whereas it has no effect on autophagy and the survival of
156 non-cancer cells [28].

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

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

170 1.3.2.Reactive Oxygen Species

171 Mitochondria is the major source of ROS. An elevated level of ROS is an important feature of cancer
172 cells, and could be attributed to mitochondrial electron transport chain activity (mainly Complex I
173 and Complex III). Increased ROS production by mitochondria in cancer cells is associated with
174 metastasis through the activation of Src and the Focal adhesion kinase Pyk2 [12]. Although a massive
175 ROS generation is mainly associated with cell damage and cell death, moderate ROS production is
176 known to activate autophagy through multiple pathways. Autophagy is activated by ROS through the
177 activation of the sensor Ataxia-telangiectasia mutated (ATM) leading to mTORC1 inhibition through
178 the LKB1/AMPK/TSC2 pathway [79]. Oxidative stress can also induce autophagy through an NFkB-
179 dependent upregulation of p62 [80]. Furthermore, ROS production is involved in starvation-induced
180 autophagy [81]. During nutrient starvation, the ROS produced regulates the activity of the HsAtg4
181 protease, which is important for phosphatidylethanolamine (PE) conjugation to LC3 [81].
182 Mitochondrial ROS can also regulate autophagy through oxidation of lysosomal membrane proteins
183 and modulation of Ca²⁺ homeostasis [82, 83]. The activation of TRPML1, a lysosomal Ca²⁺-permeable
184 transient Receptor Potential (TRP) channel, by ROS induces lysosomal Ca²⁺ release, followed by the
185 activation of calcineurin signalling, TFEB nuclear translocation and activation of autophagy and
186 lysosome biogenesis [82]. On the opposite, the activation of the lysosomal Ca²⁺ channel TRPM2 by
187 ROS induces Ca²⁺ CaMKII signalling, leading to autophagy inhibition [83]. Among ROS species, it has
188 been proposed that superoxide O₂^{•-} is the major regulator of autophagy since superoxide production
189 induced by the dysfunction of mitochondrial complexes I and III activates autophagy [84].

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

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

204 1.3.3.Mitochondrial-Associated ER Membranes (MAM)

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

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

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

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

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

257

258 2. Targeting mitophagy in cancer

259 2.1. Mitophagy regulation and function

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

267 [101]. In normal conditions, the voltage-dependent translocation of PINK1 to the IMM induces its
268 cleavage by the mitochondrial protease PARL. When IMM is depolarized, PINK1 accumulates in the
269 outer mitochondrial membrane (OMM) where it phosphorylates the E3 ubiquitin ligase Parkin,
270 leading to its recruitment at the OMM [102]. Several mitochondrial proteins, including VDAC1, Miro,
271 Mfn-1 and Mfn-2, are ubiquitinated by Parkin [103] and recognized by LC3-interacting proteins p62,
272 NDP52, optineurin, TAX1BP1 or NBR-1 to recruit the autophagic machinery [104-108]. Mitophagy is
273 also activated by hypoxia through the induction of adaptor proteins: BNIP3, NIX (or BNIP3L) and
274 FUNDC1. These proteins are localized in the OMM and contain an LC3-interacting motif to promote
275 the recruitment of the autophagic machinery [109]. The expression of BNIP3 and NIX is increased by
276 hypoxia through Hypoxia-inducible factor (HIF-1) [110, 111] whereas FUNDC1 is dephosphorylated in
277 hypoxia by Src kinase inactivation, increasing its affinity for LC3 compared to phosphorylated
278 FUNDC1 [112]. In addition, AMPK activation by low nutrient availability can directly activate
279 mitophagy through phosphorylation of Ulk1 [20].

280 Besides the activation of PINK1/Parkin and BNIP3/NIX/FUNDC1 pathways, mitophagy is highly linked
281 to mitochondrial function, enabling to equilibrate mitochondrial degradation with mitochondrial
282 activity requirement. Mitophagy is activated by OXPHOS activity to stimulate the renewal of
283 mitochondria and maintain their efficiency [113]. In addition, mitophagy induces the translocation of
284 Nrf2 and TFE3 transcription factors to the nucleus, inducing the transcription of autophagy, lysosome
285 and mitochondria-related genes to renew lysosomal and mitochondrial compartments [114].
286 Furthermore, the recognition of injured mitochondria for degradation through mitophagy is
287 regulated by mitochondrial membrane composition. In normal condition, cardiolipins, specific
288 mitochondrial phospholipids, are mostly located in the IMM. Cardiolipin externalization to the OMM
289 leads to its interaction with LC3 and acts as an elimination signal for mitophagy [115]. The hexameric
290 intermembrane space protein, NDPK-D, has been identified as the cardiolipin translocation system, in
291 case of mitochondrial depolarisation, which is needed for the elimination of damaged mitochondria
292 by mitophagy [116].

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

300

301 2.2. Mitophagy in cancer

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

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

333 In several cancer types, the degradation of damaged mitochondria and the recycling of metabolic
334 precursors by mitophagy can promote cell survival and protect from cell death [110] [136]. In Parkin-
335 deficient mice melanoma growth and metastasis are suppressed, suggesting a pro-tumour role of
336 Parkin-dependent mitophagy [137]. However, Parkin is often downregulated in many tumour types.
337 It has been recently demonstrated that besides this frequent loss of parkin, PINK1-dependent
338 mitophagy can be functional through the induction of the E3 ubiquitin ligase ARIH1/HHAR [138].
339 Interestingly ARIH1 is overexpressed in breast and lung cancer cells while Parkin expression is low
340 [138]. In addition, BNIP3 induction has been reported to promote cell migration through
341 cytoskeleton remodelling [139], resistance to anoikis [140] and invasion [141], suggesting a role of
342 BNIP3-dependent mitophagy in metastasis formation. The pro-survival role of mitophagy has also
343 been associated with resistance to anti-cancer treatments, such as the ARIH1-PINK1 mitophagy
344 which protects against cisplatin-induced cell death [138]. A role of mitophagy in resistance to anti-
345 cancer treatment is also suggested in a study showing that doxorubicin induces the expression of NIX
346 in cancer stem cells and promotes resistance to treatment through limitation of ROS production
347 [142]. Interestingly, FUNDC1 silencing has been proposed to improve chemotherapy efficiency by
348 increasing cisplatin-induced cell death [143].

349 Consistently with the dual role of mitophagy in cancer progression, the expression of mitophagy
350 proteins has been found to be either downregulated or overexpressed in different cancer types.
351 BNIP3 has been found downregulated in invasive ductal carcinoma and metastases [144] and in
352 pancreatic cancers [131, 132] but upregulated in breast ductal carcinoma *in situ* [145] and in other
353 human cancer tissues (ovarian, head and neck squamous cell carcinoma) where BNIP3 localized in
354 perinecrotic regions [111]. It has been suggested that some of these mitophagy proteins can be used
355 as prognosis markers in specific cancers. A high expression of FUNDC1 has been associated with poor
356 prognosis in cervical cancer [143]. High BNIP3 expression can be used as a prognosis marker in
357 specific cancers such as uveal melanoma where a high BNIP3 expression is associated with a poor
358 prognosis [146]. However, there is a controversy concerning the role of BNIP3-dependent mitophagy
359 in cancer that could be explained by an alternatively spliced BNIP3 expressed preferentially in cancer
360 cells: whereas the full-length BNIP3 promotes cell death, the Bnip3 Δ ex3 isoform promotes cell
361 survival [147]. Interestingly, a switch towards a glycolytic metabolism increases the expression of the
362 Bnip3 Δ ex3 isoform [147].

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

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

380

381 3. Mitochondrial calcium transporters as new targets for autophagy / mitophagy 382 modulation

383 The OXPHOS activity leads to a strong proton concentration in the intermembrane space (IMS) and is
384 the main factor that determines the very negative voltage (Ψ_m) of the IMM. Therefore the
385 modulation of OXPHOS activity can influence the proton gradient and consequently the IMM
386 potential. The electrochemical gradient in the IMS is favourable to cation influx (mainly K^+ and Ca^{2+})
387 into the mitochondrial matrix and regulates the activity of mitochondrial enzymes, ROS and ATP
388 production. This cation fluxes is tightly regulated by the expression of ion channels in the IMM: BK_{Ca} ,
389 K_{ATP} , Kv1.3, MCU, SK-family members, TRP-family members, CLIC4 and others, while the main actor in
390 the OMM that allows ion flux is VDAC [96, 97, 150, 151] (Figure 1). An interruption of cation fluxes
391 decreases OXPHOS activity and on the opposite a high cation influx induces mitochondrial membrane
392 depolarization [152, 153]. Since autophagy and mitophagy are linked with mitochondrial function,
393 the modulation of mitochondrial ion channels could be an interesting strategy to modulate
394 autophagy or mitophagy in tumours. Indeed, mitochondrial depolarization induces mitophagy
395 through the PINK1/Parkin pathway [101, 102] and the disruption of mitochondrial potential by FCCP
396 and CCCP activates autophagy and mitophagy through Nrf2 pathway and TFEB transcription factor
397 [154]. Therefore the inhibition of cation flux could have a dual effect in reducing mitochondrial
398 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

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

446

447 Conclusion

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

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470 Conflict of interests

471 Authors declare no conflict of interest.

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478 Finally, we wish to apologize to all researchers whose relevant works, owing to the limited length of
479 this article format, could not be cited in this review.

480 Figure legend

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

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

509

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