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1 **What sustains the multidrug resistant phenotype beyond ABC transporters? Looking**  
2 **beyond the tip of the iceberg**

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20

21 **Abstract**

22 ATP Binding Cassette (ABC) transporters are considered a cause of multidrug resistance

23 (MDR). However, their relevance in patients' chemoresistance and the long series of

24 unsuccessful trials with ABC transporters inhibitors have pointed out that likely they are not

25 the only cause of MDR. Several additional mechanisms evolve in cancer cells under sustained

26 stress and extensive metabolic and proteomic instability induced by chemotherapy. These *not*  
27 *oncogenic* adaptive responses induce MDR, as they provide additional means for continuous  
28 energetics supplementation and survival.

29 In this review we dissected the changes occurring in energetic and oxidative-reductive  
30 metabolism, along with the alterations of mitochondria, endoplasmic reticulum, proteasome  
31 and lysosome functions in multidrug resistant cells. We discuss how the MDR phenotype  
32 evolves as result of is the result of a complex and coordinated metabolic and organelle  
33 reprogramming, which supports the expression and activity of ABC transporters and other  
34 mechanisms of resistance. We provide examples illustrating that a higher plasticity of such  
35 reprogramming correlates with an increased ability of cancer cells to survive in stressing  
36 conditions and acquire a multi-stress resistant phenotype.

37 Understanding the molecular mechanisms and hallmarks of such coordinated cellular  
38 reprogramming will improve our knowledge on the key events determining the acquisition of  
39 resistance, and will open the way to a broad spectrum of new multitarget pharmacological tools  
40 against multidrug resistant cells.

41

## 42 **Keywords**

43 ATP binding cassette transporters; oxide-reductive metabolism; mitochondria; endoplasmic  
44 reticulum; proteasome; autophagy; lysosomes

45

## 46 **1. Introduction**

47 The concept of cancer multidrug resistance (MDR) is commonly associated with the presence  
48 of drug efflux transporters on the cell membrane that extrude drugs with unrelated structure  
49 and functions, such as chemotherapeutic agents, tyrosine kinase receptor (TKR) inhibitors, and  
50 small molecules. Most transporters belong to the ATP Binding Cassette (ABC) Transporters,

51 i.e. multi-span membrane transporters that have two ATP-binding domains as well as multiple  
52 drug-binding domains. The comprehensive analyses of Tissue Cancer Gene Atlas (TCGA)  
53 available databases (<https://cancergenome.nih.gov>) allowed to correlate the expression of  
54 several members of ABC transporters family with the resistance to specific substrates (Briz et  
55 al., 2019), although only the expression of P-glycoprotein (Pgp/ABCB1), encoded by *mdr1*  
56 gene, Breast Cancer Resistance Protein (BCRP/ABCG2) and Multidrug Resistance Related  
57 Protein 1 (MRP1/ABCC1) has been clearly correlated with clinical chemoresistance (Fletcher  
58 et al., 2016). Besides their role in chemoresistance, ABC transporter members have several  
59 physiological functions in detoxification and catabolite excretion, and are involved in cancer  
60 cell proliferation, migration and stemness (Fletcher et al., 2010; Begicevic and Falasca, 2017).  
61 These evidence have shifted the concept of ABC transporters from pure drug efflux proteins to  
62 modulators of different cellular functions that make cancer cells more aggressive and/or more  
63 prone to adapt and survive in unfavorable conditions, serving as detoxifiers and homeostatic  
64 controllers.

65 In this perspective ABC transporters should be considered as hallmarks of a cancer phenotype  
66 more resilient to stressors. Such resiliency increases cancer aggressiveness and decreases the  
67 likelihood of an effective eradication (Hanahan and Weinberg, 2011a). Resistance to stress  
68 including chemotherapy is also supported by several adaptations in cell metabolism (Vidal et  
69 al., 2018); (Icard et al., 2018), as well as in the altered functions of key cellular organelles, such  
70 as mitochondria (Valcarcel-jimenez et al., 2017), endoplasmic reticulum (ER) (Maurel et al.,  
71 2015), lysosomes (Zhitomirsky and Assaraf, 2016).

72 In this review, we will discuss how these intracellular changes support the functions of ABC  
73 transporters, and how the transporters' activity and expression can be reduced by rewiring  
74 specific energetic and oxidative-reductive metabolic pathways, or molecular circuitries  
75 connecting mitochondria, ER and lysosomes in resistant cells.

76

## 77 **2. A high metabolic plasticity favors multidrug resistance**

78 Physiologically, ABC transporters pump metabolites and drugs against their concentration  
79 gradients, at the expense of ATP hydrolysis (Fletcher et al., 2016). This process must be  
80 supported by an adequate energy supply.

81 Normal cells use the tricarboxylic acid (TCA) cycle for the catabolism of glucose, glutamine  
82 and fatty acids. In this process, oxidative phosphorylation (OXPHOS), which takes place  
83 within mitochondria, yields more than 30 ATPs from a single molecule of glucose (Vander  
84 Heiden et al., 2009). This process is enabled by the mitochondrial electron transport chain  
85 (ETC) that accepts electrons from reduced nicotinamide adenine dinucleotide (NADH) and  
86 flavin adenine dinucleotide (FADH<sub>2</sub>) (Genova and Lenaz, 2014). Cancer cells need a  
87 continuous supply of nutrients (glucose, glutamine and essential amino acids) in order to obtain  
88 building blocks for macromolecules. Consequently, they use intermediates from both  
89 glycolysis and TCA cycle to synthesize nucleotides, proteins and lipids required for tumor  
90 growth (Anderson et al., 2018). Recent studies have shown that the benefit of aerobic glycolysis  
91 (the so-called “Warburg effect”), which is far less efficient than OXPHOS, is not merely  
92 limited to the production of ATP, but is linked to the generation of intermediates necessary for  
93 anabolic processes (Hosios et al., 2016; Lunt and Vander Heiden, 2011). In multidrug resistant  
94 cancer cells, the need for anabolic metabolites is coupled with the increased need of ATP  
95 supply from both glycolytic and OXPHOS origin (Zhou et al., 2012). Therefore,  
96 chemoresistant cells display a higher ability of exploiting these two energetic routes, resulting  
97 in increased ATP amounts that are available for ABC transporters.

98

### 99 **2.1. Glycolysis-based metabolic reprogramming increases multidrug resistance**

100 The Warburg effect has been extensively correlated with the increase in chemoresistance, by  
101 pleiotropic mechanisms (Icard et al., 2018). These observations may appear counter-intuitive,  
102 since the lower OXPHOS-based metabolism, observed in highly glycolytic cells, limits the  
103 availability of ATP for ABC transporters. However, by limiting the amount of ATP and citrate,  
104 two allosteric inhibitors of glycolysis at the phosphofructokinase step, the low OXPHOS  
105 prevents the inhibition of glycolysis, grants a continuous glycolytic flux and determines a  
106 constant – although less efficient – synthesis of ATP. The preservation of constant intracellular  
107 levels of ATP is of paramount importance in maintaining chemoresistance (Zhou et al., 2012),  
108 while ATP depletion, e.g. using the hexokinase II (HKII) inhibitor 3-bromopyruvate, induces  
109 a significant sensitization to doxorubicin (Xu et al., 2005; Zhou et al., 2012).

110 Yet, the ATP crash induced by decreased glycolysis is not the only reason explaining  
111 chemosensitization. For instance, HKII induces resistance to cisplatin in ovarian cancer by  
112 activating extracellular signal-regulated kinase1/2 (ERK1/2) that mounts a protective  
113 autophagic response (Zhang et al., 2018), exploiting an ATP-dependent and ABC transporters-  
114 independent mechanisms. Another consequence of the high glycolytic flux is the increased  
115 acidification of tumor microenvironment that is associated with intracellular alkalization. This  
116 condition preserves the activity of glycolytic flux (Icard et al., 2018), favors the catalytic  
117 activity of Pgp/ABCB1 that reaches the maximal catalytic efficiency (Äänismaa and Seelig,  
118 2007), limits the membrane uptake of drugs that are weak bases such as anthracyclines (Webb  
119 et al., 2011) and increases their immediate sequestration within lysosomes (Zhitomirsky and  
120 Assaraf, 2016). The combination of the decreased import and the increased efflux strongly  
121 contributes to the maintenance of a drug resistant phenotype.

122 The Hypoxia Inducible Factor-1 $\alpha$  (HIF-1 $\alpha$ ) is a potent driver of the Warburg effect and its  
123 degradation is prevented by low oxygen tension (Semenza and Semenza, 2013). HIF-1 $\alpha$  is  
124 activated in the bulk of solid tumors and in particular in niches favorable to tumor growth, such

125 as the bone marrow of multiple myeloma. As HIF-1 $\alpha$  is a strong transcriptional inducer of  
126 several glycolytic genes (Semenza and Semenza, 2013), it creates cellular conditions that favor  
127 chemoresistance. These mechanisms have been incriminated for the resistance to bortezomib  
128 in multiple myeloma, that is reversed by the down-regulation of HIF-1 $\alpha$  and lactate  
129 dehydrogenase A (LDH-A), a HIF-1 $\alpha$ -target gene (Maiso et al., 2015)..

130 The high rate of glycolysis in many tumors is paralleled by the over-expression of the pyruvate  
131 kinase isoform M2 (PKM2). Similarly to LDH-A, PKM2 is increased in doxorubicin-resistant  
132 breast cancer cells and promotes chemoresistance: its silencing, as the inhibition of glycolysis  
133 with 2-deoxyglucose, overcomes the doxorubicin resistance mediated by Pgp/ABCB1 (Qian et  
134 al., 2018). This sensitization can be due either to the altered intracellular pH (Webb et al., 2011)  
135 or to the effects of the PKM2 dimer as a transcriptional modulator. Indeed, PKM2s cooperate  
136 with HIF-1 $\alpha$  as a transcriptional co-activator (Li et al, 2014). Since HIF-1 $\alpha$  is a strong  
137 transcriptional inducer of the *mdr1* gene (Comerford et al., 2002), PKM2 may increase  
138 doxorubicin resistance by increasing the expression of Pgp/ABCB1. Although the silencing of  
139 *mdr1* or PKM2 separately are sufficient to restore the sensitivity to paclitaxel in Pgp/ABCB1  
140 expressing ovarian cancer cells, their concomitant silencing acts in an additive way (Talekar et  
141 al., 2015). These findings suggest that Pgp/ABCB1 and PKM2 may induce resistance by  
142 independent mechanisms, e.g. the transcriptional induction of *mdr1* and and cancer cells  
143 dependence on glycolysis.

144 The PK step is a turning point in determining chemosensitivity or resistance linked to  
145 glycolysis. Indeed, if the flux of glucose to pyruvate is blunted, cells are sensitized to  
146 Pgp/ABCB1 substrates (Xu et al., 2005; Qian et al., 2018), while they become more resistant  
147 if treated with an excess of pyruvate (Wartenberg et al., 2010) that pushes the metabolic flux  
148 through the PK step. Similarly, low doses of the LDH inhibitor oxamate sensitize leukemic  
149 cells to doxorubicin, by preventing the doxorubicin-induced increase in HIF-1 $\alpha$  and

150 Pgp/ABCB1 (Zhang et al., 2018), and likely by changing pH homeostasis. On the contrary,  
151 high doses of oxamate, which completely block LDH by inducing the accumulation of  
152 pyruvate, produce the opposite effects, consistently with the observation that raising levels of  
153 pyruvate induce chemoresistance (Wartenberg et al., 2010).

154 Besides HIF-1 $\alpha$ , other transcription factors can act in parallel, reprogramming cell metabolism  
155 and up-regulating ABC transporters. For instance, the constitutive activation c-myc driven by  
156 Akt (protein kinase B)/mTOR (mammalian target of rapamycin) has been correlated with  
157 increased chemoresistance, owing to the properties of activating pro-survival/anti-apoptotic  
158 pathways and upregulating glycolytic genes at the same time (Vanderweele and Rudin, 2005;  
159 Zhang et al., 2017). In non-small cell lung cancer cells the melanoma-specific cell adhesion  
160 molecule (MCAM) up-regulates MRP1/ABCC1 and promotes a high glycolytic flux upon the  
161 activation of phosphoinositide 3-kinase (PI3K)/Akt pathway (Tripathi et al., 2017). In this way,  
162 cells are equipped of different “weapons” – increased efflux transporters, ATP supply and pro-  
163 survival pathways – orchestrating the induction of the simultaneous resistance to doxorubicin,  
164 etoposide and cisplatin (Tripathi et al., 2017).

165 Nonetheless, the question of how the oscillations in blood glucose – naturally occurring in the  
166 mammalian tissues – impact on chemoresistance remains controversial. Paradoxically,  
167 lowering the supply of exogenous glucose, mimicking thus the physiological oscillations in  
168 glycemia, can both decrease or increase the ABC transporter functions in preclinical models.

169 On the one hand, resistant cells adapt to glucose deprivation by using alternative fueling energy  
170 and increasing the expression of the glucose-regulated protein 78 (GRP78)-dependent anti-  
171 apoptotic pathways (Lee, 2007). On the other hand, lung and prostate cells with an acquired  
172 resistance to paclitaxel are more resistant in the presence of a cell culture medium enriched  
173 with glucose that fuels their main energy source, namely glycolysis (Aldonza et al., 2017). In  
174 these resistant cells the Forkhead box O3a (FOXO3a) transcription factor, which is a driver of



175 glycolysis and an inducer of Pgp/ABCB1, is constitutively active. Therefore, targeting the  
176 FOXO3a-induced glucose catabolism through glycolysis can reduce the amount of ATP  
177 available for ABC transporters and at the same time down-regulate the Pgp/ABCB1 expression  
178 (Aldonza et al., 2017). We may speculate that sensitive cells with the highest ability to adapt  
179 to either glucose deprivation or glucose supply are likely the most prone to acquire a resistant  
180 phenotype when exposed to chemotherapy selective pressure.

181

## 182 **2.2 Oxidative phosphorylation plasticity mediates multidrug resistance**

183 Besides high levels of glycolysis, increased OXPHOS rates is also a metabolic signature of  
184 multidrug resistant cells. OXPHOS-based metabolism yields higher amounts of ATP although  
185 at a slower rate than via glycolysis. Glycolysis-derived ATP can be important when cancer  
186 cells must efflux an acute bolus of chemotherapeutic drugs rapidly, while OXPHOS-derived  
187 ATP could be important to provide a continuous fueling of ATP for ABC transporters in case  
188 of prolonged exposure to the drugs. In line with this speculation, replenishing colon cancer  
189 cells with exogenous ATP that blocks glycolysis and destabilizes HIF-1 $\alpha$  abrogates the  
190 resistance of colon cancer cells to an acute pulse of oxaliplatin and 5-fluorouracil (Zhou et al.,  
191 2012), interrupting the rapid ATP supply for ABC transporters. In a complementary  
192 perspective, Pgp/ABCB1-expressing breast cancer cells, characterized by an intense OXPHOS  
193 metabolism, were insensitive to prolonged high doses of doxorubicin; in this case, doxorubicin  
194 is likely buffered by the continuous supply of ATP generated by OXPHOS and exploited by  
195 ABC transporters. Curiously, the same cells were killed by two short pulses of the drug at a  
196 lower dosage, that require an immediate supply of ATP provided by glycolysis (Riganti et al.,  
197 2015a). Mechanistically, the metronomic administration of two low doses/short pulses of  
198 doxorubicin deranges OXPHOS more than one single higher and prolonged dose, disrupting a  
199 metabolic vicious circle that is functional to sustain the Pgp-mediated resistance to high and

200 continuous doses of the drug. Different populations of U-2OS osteosarcoma cells,  
201 characterized by increasing degrees of doxorubicin resistance and Pgp expression after the  
202 selection in a medium with increasing concentrations of doxorubicin, show a progressive  
203 increase in the TCA cycle, fatty acid  $\beta$ -oxidation and OXPHOS (Buondonno et al., 2016).  
204 These findings support the hypothesis that expelling high doses of chemotherapeutic drugs  
205 requires high levels of ABC transporters but also the ability of cancer cells to reprogram their  
206 metabolism towards an increased OXPHOS and OXPHOS-dependent ATP production.  
207 Consistently, disrupting the energetic flux through the TCA cycle and OXPHOS by specific  
208 inhibitors (Bergaggio et al., 2019) or by mitochondrial-vectorised chemotherapeutic drugs  
209 (Buondonno et al., 2016), are effective means to re-sensitize the most chemoresistant cells by  
210 producing an ATP crisis. These findings indicate a sort of OXPHOS-addiction in ABC  
211 transporter-expressing cells and open new ways of inducing synthetic lethality in these cells,  
212 by combining classical chemotherapy with TCA/OXPHOS inhibitors.

213 Besides the increased production of ATP, specific mechanisms dependent on OXPHOS  
214 activity provide additional pathways of resistance. For example, the inhibition of glycolysis  
215 along with the activation of OXPHOS, achieved by silencing the metabolic mitochondrial gate-  
216 keeper tumor necrosis factor receptor-associated protein 1 (TRAP1) induces cisplatin  
217 resistance in ovarian cancer. The decrease in glycolysis and the increase in OXPHOS is  
218 associated to a higher production of interleukin-6 (IL-6), a transcriptional inducer of the drug  
219 efflux transporters Pgp/ABCB1 and Transporter Associated with Antigen Processing  
220 1(TAP1/ABCB2) (Matassa et al., 2016). Yet, we cannot exclude that other OXPHOS-linked  
221 mechanisms are also involved in cisplatin resistance: indeed, an efficient OXPHOS decreases  
222 the availability of oxygen, limiting the possibility of inducing oxidative damage by cisplatin.

223 A direct involvement of OXPHOS in ABC expression is also reported in acute myeloid  
224 leukemia, but in this case the p53 status is a determinant factor: while in wild-type p53 cells,

225 an active OXPHOS decreases the expression of Pgp/ABCB1, MRP1/ABCC1, MRP5/ABCC5  
226 and BCRP/ABCG2, the opposite trend occurs in p53-mutated or deleted cells (Gu et al., 2010;  
227 Belkahla et al., 2018). The production of reactive oxygen species (ROS) through OXPHOS  
228 may activate redox-sensitive transcription factors, such as nuclear factor-kB (NF-kB),  
229 FOXO3a and nuclear factor erythroid 2-related factor 2 (Nrf2) that up-regulate several ABC  
230 transporters (Scotto, 2003; Ji et al., 2013). Additionally, OXPHOS increases the expression of  
231 ERK5, which regulates the expression of several HIF-1 $\alpha$ -target genes (Lopez-Royuela et al.,  
232 2014), including the *mdr1* gene. These pleiotropic mechanisms provide multiple linkages  
233 between OXPHOS-based metabolism and the expression of ABC transporters. Since the  
234 promoters of each ABC transporter may have different architecture, p53 status may exert  
235 opposite effects, depending on the promoter plasticity and on the presence of different  
236 transcription factors. This plasticity may explain why OXPHOS can be either associated with  
237 increased or decreased expression of ABC transporters.

238 A high OXPHOS metabolism characterizes a subpopulation of the so-called “energetic cancer  
239 stem cells” (eCSC) in breast cancer (Fiorillo et al., 2019): these cells are resistant to classical  
240 chemotherapeutic drugs substrates of ABC transporters (Farnie et al., 2015), and are associated  
241 with clinical chemoresistance and poor outcome (Fiorillo et al., 2019). The OXPHOS inhibitor  
242 diphenyleneiodonium chloride effectively eradicates this population, reducing the probability  
243 of tumor relapse and progression. Also in patient-derived colonospheres the exposure to  
244 oxaliplatin and 5-fluorouracil increases mitochondrial biogenesis and boosts OXPHOS, by  
245 activating the histone deacetylase sirtuin-1 (SIRT1) and its substrate peroxisome proliferator-  
246 activated receptor gamma coactivator 1- $\alpha$  (PGC1 $\alpha$ ), a strong inducer of mitochondrial  
247 biogenesis (Vellinga et al., 2015). Preventing SIRT-1 activation re-sensitizes xenografts and  
248 colonospheres to chemotherapy (Vellinga et al., 2015), suggesting that preventing the increase

249 in mitochondrial number and metabolic activity is needed to overcome chemoresistance of  
250 cancer stem cells in solid tumors.

251 An active OXPHOS determines not only resistance to chemotherapy, but also to endocrine  
252 therapy (tamoxifen) in estrogen receptor-positive breast cancer cells. Indeed, tamoxifen  
253 induces oxidative stress associated with increased mitochondrial biogenesis and OXPHOS.  
254 Resistant cells have shown an increased expression of NAD(P)H dehydrogenase quinone 1  
255 (NQO1) (Fiorillo et al., 2017), an enzyme that supplies reduced ubiquinone to the electron  
256 transport chain (Li et al., 2014). The NQO1 inhibitor dicoumarol reverses tamoxifen resistance  
257 (Fiorillo et al., 2017), by preventing an increase in the OXPHOS induced by tamoxifen as well  
258 as the emergence of resistant clones able to reprogram their metabolism boosting OXPHOS.  
259 Furthermore, an active OXPHOS, associated with an increased mitochondrial biogenesis,  
260 provides a metabolic phenotype that seems to be important for the acquisition of resistance to  
261 BRAF inhibitors such as vemurafemib (Zhang et al., 2016). Specifically, in melanoma cells  
262 with oncogenic activated BRAF, the treatment with vemurafemib increases OXPHOS by  
263 enhancing the PGC1 $\alpha$ -mediated mitochondrial biogenesis (Haq et al., 2013). This process  
264 generates a population of ATP-rich and slow-cycling cells, which are resistant to mitogen  
265 activated protein kinase (MAPK) inhibitors.

266 Overall, since cancer cells are subjected to rapid changes in their micro-environment,  
267 including changes in glucose and oxygen supply, the possibility to survive and counteract  
268 stressors like chemotherapy, largely depends on their ability to reprogram their energetic  
269 metabolism, i.e. shifting between anaerobic glycolysis and OXPHOS-based metabolism.  
270 Mitochondrial metabolism is heterogeneous within solid tumors, depending on the cancer cells  
271 distance from vasculature and oxygen supply (Hensley et al., 2016). Such heterogeneity and  
272 the ability to shift between mitochondria-dependent and mitochondria-independent energy  
273 metabolism determines responses to different therapies, including anti-tumor targeted-

274 therapies (Zhang et al., 2016), anti-angiogenic therapies (Pisarsky et al., 2016) or classical  
275 chemotherapy. For instance, A549/MDR cells, have constitutively active both the  
276 Ras/ERK1/2/HIF-1 $\alpha$  axis, which increases the transcription of *mdr1* and the glycolytic flux,  
277 and the OXPHOS. By relying on the ATP of both glycolytic and OXPHOS origin, these cells  
278 display one of the most aggressive MDR profiles (Kopecka et al., 2015). The simultaneous  
279 inhibition of the Ras/ERK1/2/HIF-1 $\alpha$  axis and OXPHOS completely re-sensitizes these cells to  
280 chemotherapeutic drugs, transported by Pgp/ABCB1, MRP1-5/ABCC1-5, BCRP/ABCG2  
281 (Kopecka et al., 2015). Similarly, 3D-growing drug-resistant MCF-7 cells are eradicated only  
282 by the combined inhibition of glycolysis with 2-deoxyglucose and OXPHOS with amytal and  
283 oligomycin (Koshkin et al., 2016), implying that targeting both anaerobic and aerobic  
284 metabolic pathways are necessary to eradicate the most resistant clones.

285 Together, these findings suggest that both glycolysis- and OXHOS-based metabolism are  
286 important in the onset and maintenance of MDR, and that cells with a high metabolic plasticity  
287 are naturally selected under the pressure of chemotherapeutic drugs, emerging as resistant  
288 populations.

289

### 290 **2.3. Adaptation to hypoxia supports a multidrug resistant phenotype**

291 Cancer cells adapted to survive in a hypoxic environment are the most chemoresistant ones.  
292 First, the activation of HIF-1 $\alpha$  favors the prevalence of glycolysis over the TCA cycle  
293 (Semenza and Semenza, 2013), as well as the extracellular acidification/intracellular  
294 alkalization that reduces the ratio between drug influx and efflux (Äänismaa and Seelig, 2007;  
295 Webb et al., 2011; Zhitomirsky and Assaraf, 2016; Cardone et al., 2005; Harguindey et al.,  
296 2005).

297 Second, the limited number of nutrients and building blocks reduces tumor cell proliferation.

298 Since chemotherapy is mainly active on highly proliferative cells, hypoxic quiescent cells are

299 hard to be eradicated (Rohwer and Cramer, 2011; Wilson and Hay, 2011). For instance, the  
300 hypoxia-mediated cell cycle arrest dramatically reduces the cellular need of folates: this  
301 metabolic reprogramming determines the down-regulation of folate transporters and enzymes  
302 involved in the nucleotide synthesis, promoting strong chemoresistance to anti-folate agents  
303 such as pemetrexed or raltitrexed in renal carcinoma (Raz et al., 2014). By contrast, cell cycle-  
304 independent drugs, such as bortezomib preserve their efficacy in hypoxic cells (Raz et al.,  
305 2014).

306 Third, many chemotherapeutic agents often act by inducing oxidative damage that is produced  
307 only with an adequate oxygen supply. Therein, the efficacy of these chemotherapeutic drugs is  
308 reduced in hypoxic cells (Sasabe et al., 2007). Intriguingly, paclitaxel, gemcitabine and  
309 carboplatin increase HIF-1 $\alpha$  activity in triple negative breast cancer cells, inducing the  
310 expansion of stem cell-enriched populations that up-regulate the cystine transporter xCT and  
311 promote the synthesis of reduced glutathione (GSH), a key anti-oxidant intracellular molecule.  
312 As discussed in the next sections, the increase in anti-oxidant defenses makes cells more  
313 resistant to stress, including chemotherapy (Lu et al., 2015). This mechanism provides a linkage  
314 between HIF-1 $\alpha$  activation and anti-oxidant defense-dependent chemoresistance, opening the  
315 way to potential combination treatments – based on HIF-1 $\alpha$  and pro-oxidant/GSH antagonists  
316 agents – as potential chemosensitizers.

317 Finally, since HIF-1 $\alpha$  is a direct inducer of the *mdr1* gene (Comerford et al., 2002), hypoxic  
318 cells have physiologically up-regulated Pgp/ABCB1. Of note, doxorubicin (Cao et al., 2013),  
319 paclitaxel and gemcitabine (Samanta et al., 2014) are strong inducers of HIF-1 $\alpha$  in triple  
320 negative breast cancer; this event triggers a vicious circle, contributing to up-regulation of  
321 Pgp/ABCB1 in response to doxorubicin and acquisition of chemoresistance. Taxanes increase  
322 the stabilization of HIF-1 $\alpha$ , which determines the transcription of Pgp/ABCB1,BCRP/ABCG2,

323 anti-apoptotic and pro-autophagic genes (Pucci et al., 2018), mounting pleiotropic mechanisms  
324 of chemoresistance.

325 Hypoxia and chemotherapy are not the only unique condition which increases HIF-1 $\alpha$ .  
326 Curiously, mitochondrial ROS also stabilize HIF-1 $\alpha$ . This mechanism is of paramount  
327 importance in triple negative breast cancer stem cells, where the pro-proliferative and anti-  
328 apoptotic myc-1 and myeloid cell leukemia-1 (MCL1) proteins favor the expansion of cancer  
329 stem cell-enriched populations that are highly chemoresistant and characterized by an increased  
330 OXPHOS-based metabolism (Lee et al., 2017). Preventing either HIF-1 $\alpha$  stabilization or  
331 OXPHOS activity may have a particular therapeutic interest limiting the expansion of  
332 chemoresistant stem cells, i.e. the hardest tumor population to be eradicated. HIF-1 $\alpha$  effects on  
333 chemoresistance are interconnected with other molecular circuitries. For instance, in  
334 colonospheres, the HIF-1 $\alpha$ -activity is induced by the hypoxic environment and along with the  
335 transforming growth factor- $\beta$ 2 (TGF- $\beta$ 2) that is secreted by cancer associated fibroblasts, they  
336 both activate GLI2, a transcription factor that promotes stemness and chemoresistance to  
337 oxaliplatin and 5-fluorouracil, by increasing the ratio of anti-apoptotic/proapoptotic protein  
338 (Tang et al., 2018).

339 These observations should be a warning against the indiscriminate use of chemotherapeutic  
340 drugs in hypoxic tumors, because the metabolic rearrangements induced by hypoxia determine  
341 multiple and interconnected mechanisms of drug resistance. A careful selection of the type of  
342 chemotherapeutic drugs, eventually associated with inhibitors of HIF-1 $\alpha$  activity, may limit the  
343 emergence of resistant clones. Since HIF-1 $\alpha$  activity is regulated by several upstream pathways  
344 (Semenza and Semenza, 2013), preventing its transcriptional activity by targeting upstream  
345 controllers, such as Ras (Kopecka et al., 2015; Salaroglio et al., 2015) and RhoA (Rigoni et al.,  
346 2015), are likely efficient strategies to down-regulate both the Pgp/ABCB1-dependent and  
347 ABC transporters-independent resistance.

348

#### 349 **2.4. An altered cytosolic redox metabolism induces multidrug resistance**

350 A controlled level of oxidants (e.g. ROS) in cancer cells plays a critical role in chemoresistance.  
351 One of the key anti-oxidant cytosolic pathways to buffer ROS is the pentose phosphate pathway  
352 (PPP) that is fueled by increased glucose uptake and consequent glucose diversion from  
353 glycolysis to PPP that provides anti-oxidant power and building blocks for the synthesis of  
354 macromolecules. Indeed, PPP possesses two branches: the oxidative branch converts glucose  
355 6-phosphate (G6P) into carbon dioxide, ribulose 5-phosphate and reduced nicotinamide  
356 adenine dinucleotide phosphate (NADPH); the non-oxidative branch regenerates glycolytic  
357 intermediates fueling the cycle. Overall, PPP maintains redox balance under oxidative stress  
358 and during increased proliferation, and supports the Warburg effect (Stincone et al., 2015).  
359 NADPH, a side product of PPP, is an essential cofactor for the synthesis of lipids and  
360 regeneration of anti-oxidative potential, while ribose-5-phosphate is a nucleotide precursor  
361 (Patra and Hay, 2014), necessary for cell proliferation and metastasis. The glucose diversion  
362 into PPP has been related to cell detachment from the extracellular matrix and migration, two  
363 processes where PPP helps cells to survive oxidative stress related to detachment process  
364 (Schafer et al., 2009), in cooperation with a metabolic reprogramming that induces increased  
365 production of lactate (Payen et al., 2016), increased OXPHOS (Porporato et al., 2014) and a  
366 horizontal transfer of mitochondria from stromal to cancer cells (Boise and Shanmugam, 2019).  
367 PPP activity is regulated by both oncogenes and tumor suppressors. For instance, oncogenic  
368 Ras up-regulates the enzymes involved in ribose-5-phosphate biosynthesis (Ying et al., 2012),  
369 while wild-type p53 directly inhibits G6P dehydrogenase (G6PD), the rate-limiting enzyme of  
370 PPP (Jiang et al., 2011), determining a finely tune range of PPP activity that depends on the  
371 mutational and oncogenic landscape of each tumor. The NADPH/NADP<sup>+</sup> ratio dictated by PPP  
372 regulates the intracellular redox homeostasis and ROS neutralization (Israël and Schwartz,



2011). NADPH produced by PPP regenerates GSH and fuels GSH-dependent enzymes. Thus, toxic peroxide species are eliminated by glutathione peroxidase (GPX) which converts 2 GSH molecules to their oxidized form (GSSG). Glutathione reductase (GR) recycles GSH, while glutathione S-transferase (GST) favors the production of GSH conjugated-products (Espinosa-Diez et al., 2015), extruded by ABC transporters. Besides GSH-dependen g enzymes, anti-oxidant defenses also rely on peroxiredoxins (PRDX) (Chae et al., 2011), thioredoxin (Trx) that reduces oxidized cysteine residues of PRDX, and thioredoxin reductase (TrxR) that reduces oxidized Trx in a NADPH-dependent manner (Lu and Holmgren, 2014). Chemoresistance does not rely only on one enzyme, but rather on the simultaneous activation of multiple anti-oxidant enzymes, as demonstrated by the concurrent increase in GSH (Traverso et al., 2013), G6PD (Cosentino et al., 2011), PRDX1, PRDX2 and PRDX3 (Nicolussi et al., 2017) in resistant cells.

Besides antioxidant defense systems, ROS play an important role in preventing chemotherapy-induced damage. Since cancer cells – in particular those being resistant to chemotherapy – are characterized by increased levels of ROS but also by increased activity of antioxidant mechanisms (Marengo et al., 2016), and thus they are rarely damaged by ROS. Intracellular ROS levels are the balance between the action of pro-oxidant (stress conditions, dysfunctional OXPHOS, radiotherapy and chemotherapy) as well as anti-oxidant factors (anti-oxidant and detoxification enzymes). The interplay between pro-oxidant and anti-oxidant pathways governs proliferation *vs.* differentiation, apoptosis *vs.* autophagy and survival *vs.* senescence. In resistant cells, ROS often act as signaling molecules that activate stress-responsive survival pathways (Janssen-Heininger et al., 2008), such as the PI3K/Akt, ERK1/2, MAPK, Jun N-terminal kinase (JNK) and protein kinase C (PKC) axes (Bubici et al., 2006; Koundouros and Pouligiannis, 2018; Rezatabar et al., 2019; Wu, 2006). ROS also influence the expression of transcription factors which induce anti-oxidant enzymes and ABC transporters, such as Nrf2,

398 activator protein-1 (AP-1), NF- $\kappa$ B, HIF-1 $\alpha$  and p53 (Görlach et al., 2015), thus providing  
399 multiple additional mechanisms for protection against chemotherapy.

400 The expression of antioxidants and phase I/II drug metabolizing enzymes is under the  
401 transcriptional control of Nrf2, that also up-regulates MRP1 (Furfaro et al., 2016) and PPP-  
402 related genes, such as G6PD, 6-phosphogluconate dehydrogenase (6PGD), transketolase  
403 (TKT) and transaldolase 1 (TALDO1) (Jaramillo and Zhang, 2013). This coordinated  
404 machinery provides excellent weapons to increase chemoresistance (Stincone et al., 2015), by  
405 targeting both GSH production and GSH-conjugating enzymes involved in detoxification and  
406 pumps. Indeed, Nrf2-expressing cells are resistant to etoposide, cisplatin and doxorubicin  
407 (Jaramillo and Zhang, 2013).

408 The linkage between redox metabolism and expression of ABC transporters, however, is  
409 controversial. Two phenotypes were identified in MDR cancer cells. The first phenotype is  
410 characterized by a high Pgp/ABCB1 expression, a low PPP rate, a low GSH level and increased  
411 ROS (Wang et al., 2018) whereas, the second one is characterized by a high Pgp/ABCB1  
412 expression, high GSH levels despite the low PPP flux and decreased ROS (Lopes-Rodrigues  
413 et al., 2017). These observations suggest a high inter- and intra-tumor variability. For instance,  
414 in a 3D model of MCF-7 breast cancer cells, the increased expression of Pgp/ABCB1 is  
415 followed by low PPP rate, decreased production of NADPH/GSH and increased ROS (Wang  
416 et al., 2018). Of note, doxorubicin-induced expression of Pgp/ABCB1 can be counteracted by  
417 the ROS inhibitor N-acetyl-L-cysteine (NAC) via the inhibition of Chk2/p53/NF- $\kappa$ B axis (Cao  
418 et al., 2013). These findings suggest that the increased ROS not buffered by PPP are the *primum*  
419 *movens* of the increased Pgp/ABCB1. In support of this hypothesis, silencing or overexpression  
420 of G6PD negatively correlates with ROS level and Pgp/ABCB1 expression (Wang et al., 2018).  
421 In partial contrast, Pgp/ABCB1-expressing non-small lung carcinoma cells NCI-H460/R and  
422 leukemia cells K562/Dox have a low PPP rate consequent to the decreased expression of

423 G6PD, 6PGD and TKT, a low expression of PRDX2 and NADPH regenerating enzymes (e.g.  
424 G6PD, 6PGD and isocitrate dehydrogenase 1 - IDH1), but surprisingly they have high levels  
425 of GSH (Lopes-Rodrigues et al., 2017). In this case, the high levels of GSH are due to the  
426 increased metabolism of methionine that supplies cysteine residues necessary for *de novo* GSH  
427 synthesis (García-Giménez et al., 2017). This phenotype also provides higher amounts of  
428 methyl groups and supports the increased ability of DNA methylation (Arrigoni et al., 2016),  
429 also implying that epigenetic changes are likely involved in the acquisition of chemoresistance.  
430 These experimental evidence suggest that multiple mechanisms, either PPP-dependent or PPP-  
431 independent, may increase the levels of GSH and favor a chemoresistant phenotype.  
432 Disrupting the balance between the PPP rate, GSH levels and ROS levels may provide new  
433 chemosensitizing strategies. For instance, the therapeutic success of purine and pyrimidine  
434 nucleotide/nucleoside analogs is hampered in cells with an active *de novo* synthesis of  
435 nucleotides (Shelton et al., 2016) that relies on PPP. Inhibiting PPP or GSH opens the  
436 possibility for synergistic intervention with the existing anti-metabolite agents. Of note, a quite  
437 unexplored purine nucleoside analog, namely sulfinosine, sensitizes MDR cancer cells to  
438 doxorubicin by lowering the GSH levels and exerting a pro-oxidant activity, coupled with the  
439 decreased expression of Pgp/ABCB1 mediated by HIF-1 $\alpha$  (Dačević et al., 2013).  
440 Inhibiting G6PD not only sensitizes cells to chemotherapy but also to targeted therapies: for  
441 instance in triple wild type (KRAS/NRAS/BRAF) multiple myeloma cells, the G6PD inhibitor  
442 6-aminonicotinamide (6AN) significantly increases the anti-proliferative efficacy of the EGFR  
443 inhibitors gefitinib and afatinib (Chen et al., 2015). The mechanism relies on the increase of  
444 ROS, because the sensitizing effects of 6AN are lost when cells are supplemented with  
445 NADPH. Similarly, the natural glucoside polydatin, a G6PD inhibitor, is synergic with the  
446 EGFR inhibitor lapatinib in MCF-7 cells, by inducing oxidative stress, activating autophagic

447 flux and ER stress-dependent apoptosis (Mele et al., 2019), counteracting other mechanisms  
448 that sustain the MDR phenotype (see Sections 4 and 5).

449 Besides blocking PPP, other therapeutic approaches that also decrease intracellular GSH  
450 include the administration of the oxidized form of vitamin C (Yun et al., 2015) or the inhibition  
451 of GSH synthesis, e.g. by inhibiting the cystine importer xCT (Dixon et al., 2014; Yang et al.,  
452 2014). These options may be considered as new chemosensitizing treatments.

453 If the inhibition of PPP is generally associated with a reversion of chemoresistance, this feature  
454 is not univocal. For instance, a recent study has shown that inhibition of G6PD can sensitize  
455 cisplatin resistant non-small cell lung carcinoma A549 cells (Hong et al., 2018). GSH depletion  
456 and consequently ROS generation were induced either by the silencing of G6PD or its  
457 pharmacological inhibition with 6-aminonicotinamide (6AN). Moreover, treatment with the  
458 antioxidant NAC preserved cisplatin resistance of A549/DDP cells silenced for G6PD (Hong  
459 et al., 2018).

460 In support of the “danger threshold” hypothesis there are evidence from clinical trials with  
461 selenium or vitamin E supplementation that yielded undesirable results by worsening cancer  
462 prognosis and survival. The explanation for negative results could be found in the fact that  
463 cancer cells possess increased ROS buffering capacity (Tew, 2016). Therefore, a lower  
464 reduction in ROS levels may reduce the amount of ROS below the “danger threshold”,  
465 promoting their role as pro-survival transducers. Quite opposite, a recent study showed that the  
466 lipophilic antioxidant coenzyme Q10 increases the sensitivity to temozolomide and suppresses  
467 the invasion of resistant glioma cells (Burić et al., 2019). The mechanism, however, is  
468 apparently unrelated to ROS-dependent mechanism, but it relies on the decreased expression  
469 of matrix metalloproteinase-9 (MMP-9), N-cadherin and vimentin ((Burić et al., 2019).

470 By contrast, there are different examples of pro-oxidant compounds that efficiently eliminate  
471 MDR cancer cells, such as metal-based anticancer agents that hugely increases ROS production

472 bypassing the “danger threshold”. For instance, ferrocene-quinidine epimers exert a strong pro-  
473 oxidant activity and induce a strong mitochondrial damage in MDR cancer cells (Podolski-  
474 Renić et al., 2017). Importantly, these compounds are more effective, alone or in combination  
475 with paclitaxel, against non-small cell carcinoma and colorectal carcinoma chemoresistant  
476 cells than against their sensitive counterparts (Podolski-Renić et al., 2017), likely because of  
477 the different redox status of resistant cells. A similar preferential cytotoxicity towards MDR  
478 cancer cells is displayed by pro-oxidant derivatives of natural occurring compounds, such as  
479 avarone, tert-butylquinone (Jeremić et al., 2016) and protoflavone (Stanković et al., 2015).  
480 Having constantly higher levels of ROS and anti-oxidant enzymes compared to chemosensitive  
481 cells, some MDR cells are able to maintain a constant control of intracellular ROS exploiting  
482 them as pro-survival and stress-resistant signal molecules. On the other hand, this condition  
483 represents an instable equilibrium: strong pro-oxidant agents may turn the positive role of ROS  
484 into a negative role, explaining the peculiar sensitivity of MDR cells to direct killing (Pluchino  
485 et al., 2012) and chemosensitizing effects of pro-oxidant agents.

486

### 487 **3. Changes in mitochondria functions support multidrug resistance**

488 As key generators of energy, mitochondria are continuously adapting to cellular needs. Having  
489 properly functioning mitochondria is essential for cell survival and mitochondrial quality  
490 control is critical for all cells (Springer and Macleod, 2016). In particular, a sub-population  
491 with a high mitochondrial mass can be isolated from primary tumors: this subset maps cells  
492 with stemness features and chemoresistance (Farnie et al., 2015), indicating that functioning  
493 mitochondria are important for self-renewal and resistance to external stresses as  
494 chemotherapy.

495 Mitochondrial dynamics, i.e. fission and fusion, together with mitophagy, represent essential  
496 processes ensuring an adequate number of mitochondria. While fission results in mitochondrial

497 fragmentation and temporarily increases the overall number of the organelles within the cell,  
498 fusion has the opposite effect. An increase in fused mitochondria decreases mitophagy,  
499 whereas an increase in mitochondrial fission is associated with increased mitophagy (Kulikov  
500 et al., 2017). Recent evidence suggest that fission, fusion and mitophagy significantly influence  
501 both cancer progression and resistance to treatment, thus playing a role in the MDR phenotype.

### 502 **3.1. Changes in the fusion and fission machinery in multidrug resistant cells**

503 Mitochondrial fission divides a single mitochondrion in two or more daughter organelles. Since  
504 mitochondria cannot be formed *de novo*, fission is essential to increase the number of  
505 mitochondria within the cell (Scott and Youle, 2010). As such, fission is a compulsory step in  
506 cell division, occurring contemporarily to mitosis (Perciavalle et al., 2012). Mitochondrial  
507 fission also has additional roles, being a stepping stone before defective mitochondria are  
508 degraded (Xie et al., 2015). Although many signals converge to modulate mitochondrial  
509 fission, the key events are mediated by the GTPase dynamin related protein 1 (Drp1) that wraps  
510 around shrunk mitochondria and, together with ER, triggers the division of the mitochondrial  
511 membranes (Lackner, 2014). The activity of Drp1 is controlled by different proteins that can  
512 phosphorylate Drp1 at three sites, i.e. Ser616 (that activates fission), Ser637 (that inactivates  
513 fission) and Ser693 (that inhibits fission during apoptosis) (van der Blik et al., 2013).  
514 Moreover, Drp1 is regulated by several mitochondrial-associated proteins such as  
515 mitochondrial receptors fission 1 (Fis1), mitochondrial fission factor (Mff), as well as  
516 mitochondrial division (MiD) 49 and MiD51 (Lackner, 2014).

517 Mitochondrial fusion is the physical merging of two originally distinct mitochondria within the  
518 same cell. It occurs both in non-dividing and dividing, cells and consists of two steps – fusion  
519 of the outer mitochondrial membrane (OMM) and fusion of the inner mitochondrial membrane  
520 (IMM). During replication, mitochondrial fusion occurs from G1 to S phase and is necessary  
521 to enter the S phase avoiding cell cycle arrest (Braganza et al., 2019). In non-dividing cells,

522 fusion is functional when it comes to sharing the contents between organelles, preventing  
523 permanent loss of essential mitochondrial components (Lackner, 2014). The key players  
524 involved in mitochondrial fusion are three members of the dynamin family, i.e. mitofusins 1  
525 and 2 (Mfn1 and Mfn2) that are present on both OMM and IMM, and optic atrophy 1 (OPA1)  
526 protein, which is located in IMM (Ruan et al., 2018).

527 The role of the mitochondrial fission/fusion dynamics in cancer cells is still controversial.  
528 Despite the high heterogeneity among different tumor types, most evidence suggest that the  
529 initial events of tumorigenesis are characterized by increased fission and decreased fusion.  
530 Malignant cells divide rapidly and require an increased number of mitochondria to daughter  
531 cells, thus favoring fission. An increased fission often activate a metabolic switch towards  
532 OXPHOS. This trait has been involved in cancer progression (Bhattacharya et al., 2016). As  
533 such, cell-based models of self-renewing glioblastoma-initiating cells have elevated activating  
534 Drp1 phosphorylation at the Ser616 site; consistently, there is a significant inverse correlation  
535 between increased Ser616 phosphorylation in glioblastoma and patient survival (Xie et al.,  
536 2015). Several breast cancer cell lines express increased levels of Drp1 that are directly  
537 correlated with metastatic potential (Zhao et al., 2013) and in breast cancer tissues studies,  
538 Drp1 staining progressively increases from *in situ* ductal carcinoma to invasive breast  
539 carcinoma (Zhao et al., 2013). Similarly, oncocytic thyroid cell tumors overexpress both Drp1  
540 and Fis1, but only Drp1 expression is directly correlated with cancer aggressiveness and  
541 migration ability (Ferreira-da-Silva et al., 2015).

542 Concurrently, mitochondrial fusion is decreased in many types of cancer cells with high fission.  
543 Mfn2 acts as a tumor suppressor gene and inhibits the Ras/ERK1/2/MAPK pathway (Chen et  
544 al., 2004), promotes mitochondria-mediated apoptosis (Guo et al., 2007) and has anti-  
545 proliferative functions (Zhang et al., 2013). A significant downregulation of Mfn2 expression  
546 has been shown in several types of solid tumors (Wang et al., 2012; Zhang et al., 2013; Cheng

547 et al., 2016), and this read out correlates with increased tumor growth (Zhang et al., 2013) and  
548 poor prognosis (Cheng et al., 2016). On the contrary, the overexpression of Mfn2 is associated  
549 with decreased migration in gastric cancer cells (Zhang et al., 2013), increased apoptosis in  
550 hepatocellular carcinomas (Wang et al., 2012), decreased proliferation and increased  
551 mitochondrial ROS (mtROS) derived by OXPHOS in lung cancer cells (Rehman et al., 2012).  
552 Inducing mitochondrial hyper-fusion by increasing Mfn2 expression decreases breast cancer  
553 cells proliferation and induces cell cycle arrest (Braganza et al., 2019).

554 Regulating mitochondrial dynamics is one of the most prominent adaptive responses to  
555 stressors like chemotherapy in cancer cells (Cheng et al., 2016). Emerging resistant  
556 subpopulations and cancer stem cells rely significantly on mitochondrial OXPHOS. This  
557 metabolic signature can be intrinsic or can be part of an adaptive response during the  
558 acquisition of chemoresistance that requires an increased mitochondrial function (Bosc et al.,  
559 2017; Lee et al., 2017). Accordingly, as a response to stressing agents, the resistant populations  
560 shift the balance of mitochondrial dynamics towards an increased fusion. This shift offers  
561 several advantages.

562 First, the increased fusion rates enhances ATP production in cases of increased energy  
563 requirement, allows for the exchange of inter-mitochondria genetic information (Perciavalle et  
564 al., 2012) and repairs mitochondrial mutated/altered DNA, a process called “functional  
565 complementation”. Through this process, mitochondria that are damaged by cytotoxic drugs  
566 are repaired, the number of dysfunctional mitochondria decrease and cells become more  
567 resistant to apoptosis (Meyer et al., 2017).

568 Second, a decreased fission – associated with increased fusion – produces larger, elongated  
569 mitochondria that are protected from autophagic degradation (Lackner, 2014). Non-fragmented  
570 mitochondria generate more ATP via OXPHOS and this metabolic phenotype may promote  
571 chemoresistance. This hypothesis has been proven by recent studies on leukemia cell lines (Han



572 et al., 2017) and gynecological cancer cell lines (Kong et al., 2015) showing that cells exposed  
573 to cisplatin up-regulate Mfn1 and Mfn2. Similarly, leukemia cells with primary resistance to  
574 cisplatin have an intrinsic up-regulation of Mfn1 and Mfn2 compared to sensitive cells. These  
575 events increase fusion, which favors the mitochondrial DNA repair from the damage induced  
576 by cisplatin (Han et al., 2017).

577 In contrast to these works, other evidence disproves that the increased fusion/reduced fission  
578 is a mechanism of chemoresistance. In fact, it was suggested that the increased fusion and the  
579 inter-mitochondrial exchange of information may determine a horizontal transfer of  
580 mitochondrial mutations, increasing the number of damaged mitochondria (Lima et al., 2018)  
581 and triggering mitochondria-dependent apoptosis. Also, since a low fusion/fission ratio reduces  
582 OXPHOS and mtROS production (Hagenbuchner et al., 2013) and low levels of ROS act as  
583 pro-survival molecules, increased fission may protect cancer cells exposed to  
584 chemotherapeutic drugs (Gorrini et al., 2013). For instance, T-cell acute lymphoblastic  
585 leukemia cells resistant to chemotherapy exhibited low ROS levels together with an increased  
586 mitochondrial fission, mediated by the MAPK/ERK1/2 pathway that activates Drp1 (Cai et al.,  
587 2016).

588 Overall, there are no clearly-defined unique mechanisms explaining the linkage between  
589 alterations in mitochondrial dynamics and chemoresistance. It is likely that cancer cells change  
590 the fission/fusion equilibrium dynamically, in accordance with their needs and depending on  
591 microenvironment-related stress and tumor/tissue type (Guerra et al., 2017). As it occurs for  
592 metabolic reprogramming, the higher the mitochondrial plasticity, the higher is the ability to  
593 survive stress, including chemotherapy. Generally, primary resistant cancer cells and cancer  
594 stem cells often favor fission over fusion, displaying a proliferative advantage. Resistant  
595 populations that emerge after chemotherapy or other stressful conditions favor fusion over

596 fission as an adaptive response to increased energy production and mitochondrial material  
597 exchange.

598 Based on the current state of knowledge, however, and given the higher variability of tumors  
599 and drugs mechanisms of action, both fission and fusion can be considered promising targets  
600 for decreasing chemoresistance, but any intervention will be highly dependent on the tumor  
601 type and stage.

### 602 **3.2. Altered mitophagy and multidrug resistance**

603 Mitochondrial autophagy or mitophagy is a selective process that degrades abnormal or  
604 excessive mitochondria, preventing the accumulation of free radicals produced by  
605 dysfunctional mitochondria (Biel and Rao, 2018). Fission is often viewed as a pre-requisite for  
606 mitophagy since it decreases the mitochondrial size and alters mitochondrial potential, while  
607 fusion reduces the rate of mitophagy (Drake et al., 2017). The Parkin/PTEN-induced putative  
608 kinase 1 (PINK1) receptor system is probably the best-investigated trigger of mitophagy.  
609 Normally, upon the loss of mitochondrial potential PINK1 binds to the OMM where it is  
610 processed (Li et al., 2017) and it recruits Parkin (PARK2), a ubiquitin E3 ligase active on the  
611 surface of depolarized mitochondria (Hamacher-Brady and Brady, 2016). All mitochondria  
612 marked for mitophagy by this system are included in a unique vacuole (the mitophagosome)  
613 that subsequently fuses with the lysosomes forming the mitophago-lysosome (Springer and  
614 Macleod, 2016). Other mitophagy regulators include the BCL2 Interacting Protein 3 (BNIP3)  
615 and its ligand BNIP3L/NIX (Aparajita H Chourasia et al., 2015; Drake et al., 2017; Hamacher-  
616 Brady and Brady, 2016).

617 Mitophagy is highly modulated in cancer cells by extracellular signals, oxygen or nutrients  
618 availability, as well as chemotherapy. In the early stages of tumor development, the loss of  
619 function in PARK2, BNIP3 and BNIP3L/NIX is a common event in several types of cancer  
620 (Shah et al., 2012; Springer and Macleod, 2016; O'Flanagan et al., 2016). The BNIP3 function

621 is impaired in human pancreatic ductal adenocarcinoma cells (Chourasia and Macleod, 2015)  
622 and the gene is also frequently deleted in triple negative breast cancer, where its loss is  
623 associated with poor prognosis (Chourasia et al., 2015). The epigenetic silencing of BNIP3 has  
624 been reported in liver and pancreatic cancers, and these events may contribute to the  
625 chemoresistance of these tumors (Calvisi et al., 2007; Erkan et al., 2005). Nevertheless, not all  
626 data support the functional linkage between mitophagy dysfunction and tumor progression,  
627 since BNIP3 has been identified at high levels in advanced and aggressive breast, lung, prostate  
628 and endometrial cancers (Hamacher-Brady and Brady, 2016).

629 There is more agreement on the fact that at advanced stages, tumors instead from inhibiting  
630 mitophagy they tend to exploit it as a survival mechanism (Biel and Rao, 2018), although the  
631 time point and the mechanisms of this shift are unknown. Degrading damaged mitochondria  
632 by mitophagy decreases ROS levels and preserves ATP levels, eliminating dysfunctional  
633 mitochondria that may waste ATP (Yan and Li, 2018). Mitophagy also grants a rapid clearance  
634 of intracellular toxins and cytotoxic catabolites (Yan and Li, 2018), subtracting it to ABC  
635 transporters. Both mechanisms are important in order to correlate increased mitophagy with  
636 chemoresistance, mechanistically. Chemotherapy itself may increase mitophagy, as it occurs  
637 in stem cells from HCT8 human colorectal cancer cells exposed to doxorubicin (Yan et al.,  
638 2017) and in glioblastoma cells exposed to bevacizumab (Hu et al., 2012a).

639 For these reasons, inhibiting mitophagy may restore chemosensitivity and several studies have  
640 assessed the effect of combining classic chemotherapeutic agents with mitophagy inhibitors.  
641 The mitochondrial division inhibitor 1 (Mdivi-1) is a Drp1 inhibitor that prevents mitophagy  
642 in a fission-dependent manner (Li et al., 2017). Mdivi-1 re-sensitizes chemoresistant cancer  
643 cells (Kong et al., 2015), restoring the sensitivity to cisplatin in resistant cholangiocarcinoma  
644 cell lines (Qian et al., 2014). Of note, the Mdivi1-cisplatin combination preferentially affects  
645 cancer cells over non-transformed cells (Tuszkorn et al., 2019), likely as a consequence of a

646 higher basal rate of mitophagy in cancer cells. Liensinine, a major isoquinoline alkaloid,  
647 prevents mitophagy by inhibiting autophagosome-lysosome fusion. Also, liensinine synergizes  
648 with doxorubicin against resistant cancer cells (Zhou et al., 2015). Interestingly, mitophagy  
649 inhibitors in monotherapy, such as betulinic acid derivatives, are more cytotoxic against  
650 multidrug resistant cells than against sensitive cells (Yao et al., 2019), supporting the idea of a  
651 direct correlation between high mitophagy and high resistance to chemotherapy.

652 On the contrary, there are studies reporting that boosting mitophagy increases apoptosis and  
653 induces chemosensitization. For instance, ceramide and ceramide analogues strongly damage  
654 the mitochondria membrane and induce mitophagy in cancer cells (Sentelle et al., 2012),  
655 reducing the resistance to crenolanib in acute myeloid leukemia (Dany et al., 2016), to  
656 sorafenib in hepatocarcinoma (Wang et al., 2019), to docetaxel in breast cancer (Yang et al.,  
657 2015), and to doxorubicin in melanoma (Chen et al., 2019). Once again, it is likely that a  
658 moderate and controlled rate of mitophagy helps cells resist extracellular stressors such as  
659 chemotherapeutics, while deregulated mitophagy leads to the undesired destruction of the  
660 energetic machinery of cancer cells. This mitochondrial crash induces cytotoxicity.

661 Taking into account all the available evidence, mitophagy appears a very promising therapeutic  
662 target to decrease chemoresistance. However, drugs targeting mitophagy must be carefully  
663 selected, since advanced tumors can either up-regulate or down-regulate mitophagy in response  
664 to cytotoxic treatments and chemotherapy itself can modulate mitophagy in order to exploit it  
665 as a protective mechanism. The choice between inhibitors or inducers of mitophagy is highly  
666 dependent on the tumor stage, the drugs used and the chemoresistance/chemosensitivity profile.  
667 Additionally, most findings have been obtained from cell-based studies and little is known  
668 about the effects of tumor microenvironment on mitophagy-related drug resistance *in vivo*.  
669 Hence, although it is generally accepted that alterations in mitophagy determine

670 chemoresistance the use of drugs targeting mitophagy as potential chemosensitizers is still far  
671 from being applicable in patients.

### 672 **3.3. Altered redox mitochondrial metabolism in multidrug resistant cells**

673 Electron leakage from mitochondrial complexes I, III (Kowaltowski et al., 2009), IV (Diaz de  
674 Barboza et al., 2017) and other enzymes (Mailloux and Treberg, 2016) may occur in  
675 physiological conditions, when 2-4% oxygen is not completely reduced (Kowaltowski et al.,  
676 2009) resulting in mtROS formation. The same event occurs in cases of OXPHOS  
677 dysfunctions, e.g. uncoupling between OXPHOS and ATP synthesis. Since mitochondria are  
678 constant sources of ROS, mtDNA is at high risk of mutations. Therefore, it is essential to have  
679 effective anti-oxidative strategies within the mitochondria to limit this threat. The key anti-  
680 oxidant enzyme related to mitochondria is a superoxide dismutase (MnSOD, isoenzyme)  
681 located in the mitochondrial matrix (Weisiger and Fridovich, 1973). MnSOD detoxifies the  $O_2^-$   
682 radical to  $H_2O_2$ . In addition to MnSOD, Cu,ZnSOD, the typical cytosolic SOD isoenzyme, has  
683 also been found in the mitochondrial intermembrane space (Kira et al., 2002) and buffers the  
684 electron leakage occurring in this site. Moreover, many anti-oxidant enzymes found in cytosol,  
685 such as GST- $\pi$  (Goto et al., 2009) and catalase (Oldford et al., 2019), are also detected in the  
686 mitochondria.

687  $H_2O_2$ , produced by SOD, can have several different fates as if it is not properly neutralized, it  
688 can further damage mitochondrial proteins/lipid/DNA, or it can exit the mitochondria, where  
689 it contributes to redox signaling.  $H_2O_2$  trafficking occurs via mitochondrial aquaporins Aqp2,  
690 Aqp8 and Aqp9 (Lee and Thévenod, 2006). In both mitochondrial matrix and cytosol,  $H_2O_2$   
691 can be neutralized by the catalase, the GPX/GR and the Trx system.

692 As the mitochondrial genome does not have genes involved in GSH synthesis, GSH is imported  
693 via voltage-dependent anion channels through the OMM, and afterwards it follows a regulated  
694 import to matrix (Calabrese et al., 2017). The transformation of GSSG into GSH is catalyzed

695 by mitochondrial GR and Txr that use NAD(P)H. This implies that an adequate supply of  
696 NADPH should be present within mitochondrial matrix (Mailloux and Treberg, 2016). These  
697 antioxidant responses are under the coordinated control of transcription factors, such as Nrf2  
698 and NF- $\kappa$ B, that activate cytosolic and mitochondrial anti-oxidant activities in response to  
699 oxidative stress.

700 Generally, cancer cells have basal levels of ROS higher than non-transformed cells (Moloney  
701 and Cotter, 2018), as a consequence of the mitochondrial stress induced by hypoxia,  
702 deprivation of nutrients or chemotherapy that do not allow for a complete reduction of oxygen  
703 by OXPHOS (Guzy and Schumacker, 2006). mtROS can favor the adaptation under stressful  
704 conditions and consequently therapy resistance (de Sá Junior et al., 2017; Moloney and Cotter,  
705 2018; Okon and Zou, 2015). The anti-oxidant systems are regulated in part by the  
706 “supply/demand principle”, meaning that an increase in ROS production triggers the  
707 upregulation of anti-oxidant enzymes. In addition, several other signals contribute to modulate  
708 the anti-oxidant systems either directly or indirectly. One of the most important factors in  
709 maintaining the redox homeostasis is the regeneration of the anti-oxidant system components  
710 by NADPH, e.g. by an active PPP, as reported above. Another stress sensors is AMP-protein  
711 kinase (AMPK) (Sanli et al., 2014) that is activated in cancer cells by transcriptional and  
712 epigenetic mechanisms (Hui et al., 2019). AMPK activates several genes involved in acute  
713 adaptation of the metabolism to stressful conditions, long-term cellular re-programming, cell  
714 cycle regulation and proliferation (Sanli et al., 2014). For instance, FOXO3a accumulates in  
715 mitochondria upon AMPK activation (Grossi et al., 2019a) during glucose deprivation  
716 (Peserico et al., 2013). Mitochondrial FOXO3a can be acetylated or deacetylated, and these  
717 events determine cell’s fate. The p300 and cAMP response element-binding protein (CREB)-  
718 binding protein (CBP) are the main acetyltransferase involved in FOXO3a acetylation that  
719 promotes apoptosis (Daitoku et al., 2011). In contrast to acetylation, deacetylated FOXO3a

720 favors the cell's survival, by increasing the transcription of anti-oxidant genes that promote  
721 ROS detoxification (Brunet et al., 2004). The main deacetylase in mitochondria is Sirt-3  
722 (Grossi et al., 2019b). Specifically, Sirt3-FOXO3a complex in mitochondria activates the  
723 transcription of catalase and MnSOD (Jacobs et al., 2008). Additionally, Sirt-3 deacetylates  
724 MnSOD and IDH2, increasing their activity (Someya et al., 2010). Mitochondrial IDH2 is  
725 important when it comes to regenerating GSH since it increases the mitochondrial pool of  
726 NADPH (Someya et al., 2010). These mechanisms dependent on Sirt-3 additively increase the  
727 mitochondrial anti-oxidant defenses, limiting the oxidative damages induced by specific  
728 chemotherapeutic agents, such as cisplatin, doxorubicin or gemcitabine (Someya et al., 2010).  
729 FOXO3a can also be regulated by phosphorylation: in colon cancer cells the phosphorylation  
730 of FOXO3a N-terminus by MEK/Erk1/2 induces its translocation to the mitochondria in  
731 response to chemotherapy (Celestini et al., 2018), triggering the chemotherapy-protective  
732 events described above. These findings strongly suggest that Sirt inhibitors may be used as  
733 pharmacological adjuvant treatments combined with chemotherapy against drug resistant  
734 tumors. Besides increasing mitochondrial anti-oxidant defenses, FOXO3a is a strong  
735 transcriptional inducer of Pgp/ABCB1 and MRP2/ABCC2 (Beretta et al., 2019). This feature  
736 provides an additional mechanism linking an altered mitochondrial redox balance with  
737 chemoresistance, mediated by the activation of FOXO3a.

738 Another proof of the interplay between mitochondrial redox balance and chemoresistance is  
739 represented by the finding that mtROS stabilize HIF-1 $\alpha$  (Sena and Chandel, 2012). Knocking  
740 down enzymes of the TCA cycle and OXPHOS suggests that complex II (Paddenberg et al.,  
741 2003), complex III (Guzy et al., 2005), TCA enzymes and to lesser extent complex I (Quinlan  
742 et al., 2014) are the main sources of mtROS stabilizing HIF-1 $\alpha$ . Since the core of solid tumors  
743 is hypoxic, it is frequent that in this region the reduction of oxygen via OXPHOS is not  
744 complete, leading to the generation of mtROS. This situation triggers a vicious circle that

745 increases the levels of HIF-1 $\alpha$ , already increased by hypoxia. Besides increasing the  
746 transcription of the *mdr1* gene (Comerford et al., 2002), HIF-1 $\alpha$  up-regulates specific genes  
747 involved in the NADPH regeneration such as serine hydroxymethyltransferase 2 (SHMT2) (Ye  
748 et al., 2014) and in GSH synthesis, such as the GSH rate limiting enzyme glutamate cysteine  
749 ligase modifier subunit (GCLM) and the cysteine importer xCT (Lu et al., 2015; Thomas and  
750 Ashcroft, 2019). This coordinated response primes cell to develop resistance to several  
751 chemotherapeutic agents, including classical chemotherapeutic drugs or targeted-therapies  
752 such as the fibroblast growth fact receptor (FGFR) inhibitors (Okon et al., 2015). Moreover, in  
753 hypoxic cells FOXO3a reduces the mitochondrial mass and oxygen consumption  
754 (Hagenbuchner and Ausserlechner, 2013), further enhancing the possibility of generating  
755 mtROS and activating HIF-1 $\alpha$ , fueling a feed-forward circuit supporting altered mitochondrial  
756 redox metabolism and chemoresistance.

757 In addition to the above mentioned pathways, it was found very recently that during oxidative  
758 stress the catalytic component of telomerase TERT relocates within the mitochondria, where it  
759 counteracts mtROS and activates a pro-survival autophagic response (Green et al., 2019). This  
760 evidence provides an additional mechanism of protection from oxidative agents. Overall, the  
761 dynamic redox homeostasis of mitochondria in chemoresistant cells triggers pathways leading  
762 either to apoptosis or survival, depending on the severity of the oxidative stress and on the  
763 interplay among different pathways. In most cases, such interplay between redox mitochondria  
764 metabolism, energetic metabolism, proliferation and apoptosis, promotes cell survival and  
765 chemoresistance, by increasing the anti-oxidant power of cancer cells and/or increasing the  
766 expression of ABC transporters.

767

#### 768 **4. Changes in endoplasmic reticulum-dependent functions and proteostasis support**

#### 769 **multidrug resistance**



#### 770 **4.1. The response to endoplasmic reticulum stress is altered in multidrug resistant cells**

771 The ER is the site where nascent proteins are folded and subjected to post-translational  
772 modifications before being delivered to the Golgi apparatus for further modifications and to  
773 their final destination. Plasma-membrane associated proteins, including ABC transporters,  
774 follow this pathway (Trowitzsch and Tampé, 2018). Each step of proteins modification is  
775 tightly controlled by the ER-associated protein degradation/ER-quality control (ERAD/ERQC)  
776 system, a complex of ER-associated proteins that sort the properly folded proteins and target  
777 for degradation the unfolded/misfolded polypeptides (Printsev et al., 2017; Hano et al., 2018).  
778 Hypoxia, nutrient deprivation, radiotherapy or chemotherapy – a range of conditions often  
779 experimented by cancer cells – induce the accumulation of unfolded/misfolded proteins within  
780 the ER lumen. This condition is sensed by GRP78 that is strictly associated to ERAD/ERQC  
781 proteins and activates three ER stress sensors, namely inositol-requiring protein 1 $\alpha$  (IRE1 $\alpha$ ),  
782 protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6). By  
783 recruiting different downstream transducers, IRE1 $\alpha$ , PERK and ATF6 mount the so-called  
784 unfolded protein response (UPR) that promotes cell survival if the ER stress is reversible or  
785 short, but induces cell death in the case of prolonged and uncontrolled ER stress (Hetz, 2012;  
786 Maurel et al., 2015).

787 Several tumors have ERAD/ERQC proteins overexpressed (Nagelkerke et al., 2014), a feature  
788 that mimics oncogene addiction. This feature may be explained by the fact that a constitutively  
789 high UPR machinery helps cancer cells to survive under unfavorable conditions, including  
790 damages induced by chemotherapy.

791 The role of UPR in promoting or counteracting MDR is highly controversial. On the one  
792 hand, evidence support the idea that increasing ER stress results in chemoresistance, as reported  
793 for the resistance to platinum-derivatives in ovarian cancer (Yamada et al., 1999), as well as to  
794 doxorubicin and vincristine in gastric cancer (Wu et al., 2018). These works, however, do not

795 clarify the exact mechanisms of sensitization, as in the first work an increased intracellular  
796 accumulation of cisplatin was observed (Yamada et al., 1999), suggesting that it may be due to  
797 an increased uptake and/or a reduced efflux by the membrane transporters. In the second work,  
798 the chemosensitizing effects of the ER stress inducer tunicamycin are due to impaired proteins  
799 glycosylation. Since Pgp/ABCB1 must be glycosylated to reach its mature form, and both the  
800 drugs tested – doxorubicin and vincristine – are Pgp substrates we can speculate that the  
801 chemosensitization was likely due to the lower glycosylation and catalytic efficacy of  
802 Pgp/ABCB1 rather than to the direct involvement of ER stress machinery.

803 Furthermore, there is no general consensus on the fact that increasing the activation of ER  
804 stress restores chemosensitivity, since some works report an opposite scenario.

805 For instance, the activation of PERK and the downstream transducer X-box binding protein 1  
806 (XBP1) determine the assembly of the complex XBP1/HIF-1 $\alpha$  (Chen et al., 2014) that may  
807 increase the transcription of the *mdr1* gene, therein triggering ER stress-associated  
808 chemoresistance. Similarly, glucose deprivation or classical ER stress inducers (thapsigargin,  
809 tunicamycin) increased the *mdr1* gene transcription via c-jun activation (Ledoux et al., 2003),  
810 linking an acute ER stress condition to the prompt development of a multidrug resistant  
811 phenotype.

812 In BRAF<sup>V600E</sup> mutated melanoma cells, cells resistant to vemurafemib activate a peculiar ER-  
813 dependent protective response. Specifically, after exposure to vemurafemib, mutated BRAF  
814 binds to GRP78 that triggers the expansion of ER and favors the activation of a protective  
815 autophagic flux, responsible for resistance (Ma et al., 2014). Under these conditions, only the  
816 use of autophagy inhibitors can reverse cell resistance to vemurafemib (Ma et al., 2014).

817 Similarly, in multiple myeloma cells GRP78 dictates the resistance to the proteasome inhibitor  
818 bortezomib by activating autophagy (Malek et al., 2014) (see also below). ER stress and ATP  
819 depletion are also associated to chemosensitization to paclitaxel in Pgp/ABCB1-expressing

820 ovarian cancer cells: in these cells, the estrogen receptor- $\alpha$  modulator BHPI produces a huge  
821 depletion of ATP that in turns triggers a UPR-dependent cell death (Zheng et al., 2018) and  
822 likely decreases the catalytic efficiency of Pgp/ABCB1, inducing at least two events that can  
823 increase the sensitivity to paclitaxel.

824 In contrast with the previous evidence, the activation of GRP78 by betulinic acid triggers the  
825 activation of the PERK/CCAAT/enhancer-binding protein homologous protein (CHOP)  
826 apoptotic pathway in breast cancer cells. This mechanisms restores the sensitivity to taxol (Cai  
827 et al., 2018). The presence of contrasting evidence on the role of ER stress as inducer or  
828 inhibitor of chemoresistance may be explained by the different stimuli that specifically activate  
829 one ER-downstream signaling over the others, by the duration of the ER stressing conditions  
830 (e.g. acute *vs.* prolonged ER stress) as well as by the pattern of ER-dependent transducers that  
831 may highly vary in different tumor types. For instance, in resistant pancreatic cells, gemcitabine  
832 resistance is associated with up-regulation of ATF4 and CHOP that exerts anti-apoptotic  
833 functions in these cells, as well as the accumulation of the phospho(Ser51)-eukariotic initiating  
834 factor 2 $\alpha$  (eIF2 $\alpha$ ) that reduces protein synthesis. This mechanism prevents the accumulation of  
835 unfolded polypeptides and ER stress-mediated cell death. By contrast, ATF4 silencing – i.e.  
836 the deprivation of a classical ER stress sensor – restores the UPR response and the sensitivity  
837 to gemcitabine in this cancer type (Palam et al., 2015).

838 Therefore, it is hard to predict a common biological phenotype linking ER dysfunctions to  
839 chemoresistance. For example, a proteomic analysis of non-small cell lung cancer cells showed  
840 that resistance to cisplatin is associated with the overexpression of IRE1 $\alpha$ , disulfide isomerase  
841 PDIA4 and PDIA6, and to the down-regulation of GRP78, PERK and ATF6 (Tufo et al., 2014),  
842 while in other tumors chemoresistance is associated to a completely different profile of ER-  
843 related proteins. Only an in-depth molecular characterization of tumor subtypes may identify

844 specific signatures predicting if a specific ER stress-related response is associated to drug  
845 sensitivity or resistance.

846 Recently, molecular mechanisms linking the resistance to ER stress and the resistance to  
847 chemotherapy have emerged in different tumors, leading to the hypothesis of a “multi-stress  
848 resistant” phenotype.

849 Cells adapted to survive under chronic non-lethal ER stress conditions (mimicking thus the  
850 conditions that occur in solid tumors) acquire the simultaneous resistance to ER stress and  
851 chemotherapy. Indeed, after a step-wise selection with different ER stress inducers  
852 (thapsigargin, tunicamycin, brefeldin A), ER stress-adapted cells increase PERK expression  
853 and PERK-dependent Nrf2/MRP1 axis, acquiring a multidrug resistant phenotype (Salaroglio  
854 et al., 2017). Notably, drugs with acquired resistance to ER stress up-regulate several UPR-  
855 related genes, but the only gene up-regulated to similar extent in the same cell line with  
856 acquired resistance to chemotherapy is PERK (Salaroglio et al., 2017), suggesting that this ER  
857 stress sensor may be the driver of a multi-stress resistant phenotype.

858 The common resistance to ER stress- and chemotherapy-dependent cell death is confirmed by  
859 complementary findings, showing that cancer cells with either constitutive or acquired  
860 resistance that express ABC transporters have reduced sensitivity to ER stress-dependent cell  
861 death (Riganti et al., 2015b). Notably, this phenotype is strictly interconnected with  
862 chemoresistance. Indeed, in chemosensitive cells ER stressing agents and chemotherapeutic  
863 drugs increase the amount of ER stress transducer CCAAT/enhancer-binding protein- $\beta$   
864 (C/EBP- $\beta$ ) LIP isoform that promotes the pro-apoptotic axis C/EBP/CHOP/caspases 3 and at  
865 the same time down-regulates Pgp/ABCB1. By contrast, chemoresistant cells are refractory to  
866 the induction of C/EBP- $\beta$  LIP, and display high levels of C/EBP- $\beta$  LAP. The latter isoform  
867 promotes cell survival and down-regulates Pgp/ABCB1 (Riganti et al., 2015b). Since the main  
868 mechanism of C/EBP- $\beta$  LIP loss is its altered ubiquitination and degradation via proteasome

869 and lysosome, the combination of proteasome inhibitors and lysosomotropic agents induce  
870 chemosensitization and cell death in response to ER stressing conditions (Kopecka et al., 2018;  
871 Salaroglio et al., 2018).

872 In a curious anti-parallelism with the mitochondrial phenotype of chemoresistant cells, the  
873 increase of resistance is associated with a progressive increase in the expression of  
874 mitochondrial energetic metabolism-related genes and with a progressive decrease in the  
875 expression of ERAD/ERQC genes. In particular, osteosarcoma chemoresistant cells have a  
876 defective ERAD/ERQC system that make them constantly subjected to a chronic ER stress.  
877 This situation promotes the basal up-regulation of pro-survival pathways that contribute to  
878 resistance to chemotherapy (Buondonno et al., 2019). However, this ER stress response  
879 represents an unstable equilibrium. Pharmacological approaches, based on disulfide-releasing  
880 doxorubicin vectorized within the ER, disrupt the defective ERAD/ERQC system of resistant  
881 cells, increasing the amount of unfolded and ubiquitinated proteins within the ER, and  
882 triggering an ER-dependent apoptosis (Buondonno et al., 2019). Such a response is less  
883 pronounced in sensitive cells that possess a functioning ERAD/ERQC system, revealing an  
884 Achille's heel of resistant cells. These data are supported by a large phenotypic and genotypic  
885 analysis of chemoresistant multiple myeloma cells present in patients with minimal residual  
886 disease, showing that chemoresistant clones – responsible of tumor relapse and poor outcome  
887 – are characterized by an intense down-regulation of ERAD/ERQC genes (Paiva et al., 2019).

888 Among the proteins that require proper folding within the ER there is the Pgp/ABCB1.  
889 Therefore, inhibiting the ERAD/ERQC system in resistant cells inevitably determines the  
890 misfolding and ubiquitination of this ABC transporter, providing an additional mechanism of  
891 chemosensitization (Buondonno et al., 2019). In agreement with this finding, Ag-nanoparticles  
892 inducing ER stress overcome drug resistance by decreasing the Pgp/ABCB1 expression

893 (Gopisetty et al., 2019). This event can be attributed to the degradation of Pgp/ABCB1  
894 following ER stress induced by the Ag-nanoparticles.

895 An altered response to ER stress has been also correlated with resistance to drugs different  
896 from conventional chemotherapeutic agents, such as bortezomib. In multiple myeloma, low  
897 levels of ATF6 and the XBP1 are markers of bortezomib resistance; also, defective ATF6 and  
898 XBP1 imply a small ER lumen and a low capacity of cells to mount a ER stress-dependent cell  
899 death in response to bortezomib (Nikesitch et al., 2018). Interestingly, the pharmacological  
900 inhibition of E1 ubiquitin-activating enzymes that act up-stream of the proteasome system  
901 increases the expression of the three ER stress sensors IRE-1 $\alpha$ , PERK and ATF6; induces an  
902 ER stress-dependent cell death and restores the sensitivity to proteasome inhibitors and  
903 chemotherapeutic agents that are unrelated for mechanisms of action, such as doxorubicin,  
904 melphalan and lenalidomide (Zhuang et al., 2019).

905 Whatever the mechanisms are, these findings support the hypothesis that resistance to ER stress  
906 and resistance to chemotherapy are often associated in cancer cells.

907 Besides its role in protein folding and inducing UPR, ER has revealed an unexpected role as  
908 drug sequestration organelle. Specifically, the 3- $\beta$ -hydroxysteroid- $\Delta$ 8, $\Delta$ 7-  
909 isomerase/emopamil-binding protein (EBP), an ER-associated enzyme physiologically  
910 involved in sterol biosynthesis, has recently displayed the properties of a multidrug binding  
911 protein, able to capture multiple anionic drugs in its central cavity (Long et al., 2019). This  
912 finding confirms that, besides plasma-membrane associated ABC transporters, other  
913 intracellular organelles and associated enzymes also strongly contribute to MDR.

#### 914 **4.2. The response to proteotoxic stresses in chemoresistant cells**

915 Proteome stability and functionality is assured in cells by the so-called proteostasis network  
916 (PN), a modular and highly integrated system that ensures proteome quality control at both  
917 basal conditions and in case of increased proteotoxic stress (i.e. conditions of elevated

918 proteome instability). PN addresses the triage decision of *fold*, *hold*, or *degrade* (Sala et al.,  
919 2017; Sklirou et al., 2018). The key functional modules of the PN are the cytosolic and ER  
920 sites of proteins synthesis, along with the machineries of proteins sorting and trafficking, the  
921 UPR machinery of the ER (UPR<sup>ER</sup>) and mitochondria (UPR<sup>MT</sup>), the intra- and extra-cellular  
922 network of molecular chaperones (also known as Heat Shock Proteins, HSPs), the  
923 compartmentalized (e.g. nuclear, cytosolic or mitochondrial) proteases, and the highly  
924 regulated degradation machineries of the ubiquitin-proteasome (UPP) and autophagy-lysosome  
925 (ALP) systems (Kaushik and Cuervo, 2015; Sklirou et al., 2018). Misfolded polypeptides  
926 tagged with ubiquitin are mainly degraded by the UPP system (Tsakiri and Trougakos, 2015).  
927 ALP activation prevails when the UPP system is overwhelmed; the HSP repairing/folding  
928 system fails resulting in the accumulation of protein aggregates or upon the extensive  
929 deterioration of cellular organelles (Tsakiri and Trougakos, 2015). Autophagy starts with  
930 autophagosome formation, followed by its fusion with lysosomes for degradation of the cargo  
931 (Klionsky et al., 2016). Moreover, proteotoxic stress regulates the activity of eIF2 $\alpha$ , which  
932 triggers a general inhibition of protein synthesis triggers and cell cycle arrest (McConkey,  
933 2017).

934 The PN modules are regulated by several transcription factors, such as Nrf2, FOXO, p53 or  
935 Heat shock factor 1 (HSF1); these transcription factors essentially function as stress sensors  
936 (e.g. during exposure to chemotherapy) and activate cytoprotective genomic responses (Sklirou  
937 et al., 2018). The Nrf2 signaling pathway plays a crucial role in the cellular defenses against  
938 oxidative and/or xenobiotic damage, by up-regulating several anti-oxidant and/or phase-II  
939 detoxifying enzymes (Sykiotis and Bohmann, 2010), UPP and ALP genes (Tsakiri et al.,  
940 2019a). Moreover, chemotherapy-mediated proteome instability triggers the HSF1-mediated  
941 activation of several chaperones that promote proper folding, unfolding and remodeling of  
942 polypeptides (Niforou et al., 2014). The key chaperones involved in proteotoxic stress are the

943 ATP-independent small HSPs (sHSPs, with a molecular weight of ~10-40 kDa) that are also  
944 referred to as “holdases”; the ATP-dependent HSP60, HSP70, and HSP90, also known as  
945 “foldases” (Saibil, 2013); the ATP-dependent disaggregases, which extract polypeptides from  
946 protein aggregates (Barends et al., 2010). All these proteostatic modules are highly integrated  
947 by extensive functional crosstalk (Tsakiri et al., 2019a) and their dysfunction has a severe  
948 impact on mitochondrial functionality (Gumeni et al., 2019) and genomic stability (Tsakiri et  
949 al., 2019b).

950 The functionality of anti-stress and proteostatic (Kaushik and Cuervo, 2015; Sala et al., 2017;  
951 Sklirou et al., 2018) responses decline during aging, favoring the onset of age-related diseases,  
952 including cancer (López-Otín et al., 2013). Indeed, aging is characterized by increased cellular  
953 levels of stressing agents and damaged biomolecules, as well as by compromised stress  
954 responses and survival pathways (Sala et al., 2017; Sklirou et al., 2018). Cancer cells are  
955 characterized by significantly higher proteome instability than non-transformed cells. Thus, in  
956 order to survive they become “addicted” to over-active proteostatic modules (Sklirou et al.,  
957 2018), developing a so-called “non-oncogenic” addiction. This cytoprotective adaptation is  
958 increased when tumor cells are under the selective pressure of anti-tumor therapy (e.g.  
959 chemotherapy, radiotherapy or targeted therapies) (Luo et al., 2009), as demonstrated for  
960 instance by the constitutive activation of HSPs in cancer cells exposed to chemotherapy  
961 (Kijima et al., 2019). In support, HSPs upregulation during therapy contribute to  
962 chemoresistance and poor prognosis (Lianos et al., 2015).

963 Consistently, targeting of HSPs (Vahid et al., 2017) or HSF1 (Kijima et al., 2019) has produced  
964 encouraging results in clinical trials. The combination of JAK2 inhibitors and HSP90 inhibitors  
965 overcome resistance to current JAK2 inhibitors in myeloproliferative neoplasias (Meyer,  
966 2017). Promising results have been reported in HER2-positive breast cancer refractory to  
967 trastuzumab and in anaplastic lymphoma kinase (ALK)-mutated lung cancers resistant to



968 crizotinib, by combining these targeted therapies with the HSP90 inhibitor 17-AAG and  
969 trastuzumab (Jhaveri and Modi, 2012; Simionato et al., 2015). Moreover, HSP90 inhibitors  
970 have shown encouraging results against tumors resistant to the early generation of tyrosine  
971 kinase inhibitors (TKIs) (Wang et al., 2016).

972 Similarly, sHSPs up-regulation is associated with poor prognosis and drug resistance (Lourda  
973 et al., 2007; Zoubeidi and Gleave, 2012). Since these chaperones are ATP-independent they  
974 are less amenable to inhibition by small molecules. Therefore, gene silencing-based strategies  
975 have been tested to inhibit sHSPs such as HSP27 and clusterin (CLU) (Ischia et al., 2013;  
976 Trougakos et al., 2009a; Trougakos and Gonos, 2009; Zoubeidi and Gleave, 2012). HSP27 has  
977 been involved in the development of gemcitabine-resistance in pancreatic cancer cells  
978 (Kuramitsu et al., 2012) and MDR in gastrointestinal tumors (Soleimani et al., 2019). CLU is  
979 activated by Akt (Zhong et al., 2010) and STAT1 (Patterson et al., 2006), and has been involved  
980 in resistance to docetaxel in prostate cancer (Zhong et al., 2010), as well as to doxorubicin,  
981 cisplatin, etoposide, camphothecin, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), tumor necrosis factor-  
982 related apoptosis-inducing ligand (TRAIL), Fas and histone deacetylase inhibitors in renal,  
983 breast, and non-small lung cancer cells (Djeu and Wei, 2009). Consistently with its  
984 chaperoning activity, CLU was found to stabilize the cytosolic Ku70/Bax complexes,  
985 inhibiting Bax pro-apoptotic activity (Trougakos et al., 2009b).

986 On another mode of action, the extensive remodeling of the HSPs network may also stabilize  
987 p53 mutations conferring oncogenic gain-of-function properties to the protein. Specifically,  
988 during adaptation to stress, HSPs unwind the mutant p53 protein that exposes aggregation-  
989 prone sites, able to sequester tumor suppressor proteins, inhibiting apoptosis and inducing  
990 chemoresistance (D'Orazi and Cirone, 2019; Wawrzynow et al., 2018).

991 Overall, cancer cells' addiction to *non-oncogenic* pathways either during carcinogenesis or  
992 following therapeutic treatment is likely a key response that maintains the MDR phenotype

993 beyond ABC transporters. Increased proteotoxic stress fuels genome instability which then  
994 further increases proteome instability due to the elevated production of mutated polypeptides,  
995 creating thus a vicious circle. By increasing genomic and proteomic instability, chemotherapy  
996 may expedite the acquisition of a resistance phenotype by up-regulating cytoprotective PN  
997 modules. This *non-oncogenic* addiction represents a hallmark essential for maintaining  
998 resistance; consequently, it can be exploited therapeutically by targeting specific proteostatic  
999 pathways. Besides HSPs inhibitors, recent approaches are based on small molecules impairing  
1000 the physiological protein quality control machinery of UPP, such as the ubiquitin E3 ligase-  
1001 guided proteolysis-targeting chimeras (PROTACs), chemical modulators of deubiquitinating  
1002 enzymes acting upstream the proteasome (Salami and Crews, 2017; Moon and Lee, 2018) and  
1003 inhibitors of the proteasome's regulatory subunits (Muli et al., 2019).

#### 1004 **4.3. The role of altered proteasome functions in multidrug resistant cells**

1005 UPP is composed of ubiquitin-conjugating enzymes and 26S proteasome; the latter consists of  
1006 a catalytic 20S core particle bound to a 19S regulatory particle (Tsakiri and Trougakos, 2015).  
1007 The 20S particle is composed of four stacked heptameric rings that form a barrel-like structure.  
1008 The caspase-, trypsin- and chymotrypsin-like peptidase activities are located at the  $\beta$ 1,  $\beta$ 2, and  
1009  $\beta$ 5 proteasomal subunits, respectively. The 19S particle is involved in substrate recognition,  
1010 de-ubiquitination, unfolding and translocation into the 20S portion (Tsakiri and Trougakos,  
1011 2015). The catalytic activity of the proteasome is crucial in protein quality control, as unfolded,  
1012 misfolded, or non-functional newly synthesized polypeptides are targeted to cytosolic or ER-  
1013 bound proteasomes (ERAD; see above) for degradation (Qi et al., 2017). Proteasomes are also  
1014 found in the nucleus and in the OMM, where during activation of the UPR<sup>MT</sup> they mediate the  
1015 so-called outer mitochondrial membrane-associated degradation (OMMAD). OMMAD  
1016 degrades damaged proteins from OMM and matrix, controlling mitochondrial proteostasis  
1017 (Baker et al., 2011). Moreover, UPP degrades mitochondrial proteins involved in fusion and

1018 fission (Wang et al., 2011; Wiedemann et al., 2013), regulating mitochondria dynamics. Since  
1019 both mitochondrial fusion and fission are important in determining chemoresistance, OMMAD  
1020 provides the functional linkage between altered mitostasis, altered proteostasis and MDR.  
1021 Proteasomal activity is significantly induced during sustained proteotoxic stress, e.g. during  
1022 tumorigenesis or exposure to chemotherapy (Skirou et al., 2018). Similarly to the non-  
1023 oncogenic addiction to proteostatic systems, cells exposed to chemotherapeutic drugs become  
1024 dependent on an efficient proteasome activity for their survival. Consistently, proteasome  
1025 inhibitors were turned out to be very effective drugs against specific malignancies, such as  
1026 multiple myeloma (Manasanch and Orłowski, 2017). Proteasome inhibitors of the first  
1027 (bortezomib) or second (carfilzomib) generation, along with the orally administered novel  
1028 agents (ixazomib), take advantage of the heavy reliance of myeloma cells on the 26S  
1029 proteasome for the degradation of excessive or misfolded monoclonal immunoglobulins and/or  
1030 free light chains produced (Bianchi and Anderson, 2019; Farrell and Reagan, 2018).

1031 Nonetheless, as for most other tumor therapies, resistance to proteasome inhibitors is often  
1032 observed in patients (Robak et al., 2018). Known mechanisms of resistance include the  
1033 increased levels of proteasomes in tumor cells, the sole overexpression of the  $\beta 5$  proteasomal  
1034 subunit PSM $\beta 5$  (Balsas et al., 2012), or even mutations in proteasomal subunits that make cells  
1035 insensitive to the inhibitors (Robak et al., 2018). Reportedly, resistance to proteasome  
1036 inhibitors may also relate to the increased UPR that overwhelms the UPR capacity (Hetz, 2012;  
1037 Maurel et al., 2015), to the accumulation of aggresomes that up-regulate protective autophagic  
1038 responses (see below), to the aberrant activation of pro-survival signaling pathways (Niewerth  
1039 et al., 2015), to the defective apoptosis, senescence and DNA repair mechanisms (Dolloff,  
1040 2015; Wallington-Beddoe et al., 2018), and to the induction of Pgp/ABCB1 (Abraham et al.,  
1041 2015). Interestingly, at a systemic level resistance to proteasome inhibitors may be also caused

1042 by the horizontal transfer of PSMA3 and PSMA3-AS1 proteasome subunits via extracellular  
1043 vesicles (Xu et al., 2019).

1044 The high activity of proteasome is also likely involved in the maintenance of chemoresistance  
1045 in solid tumors (Roeten et al., 2018), likely using the same pleiotropic mechanisms observed  
1046 in multiple myeloma. Disappointingly, the promising preclinical data obtained with bortezomib  
1047 in models of solid tumors have not been confirmed in patients (Guerrero-Garcia et al., 2018).  
1048 Nonetheless, the question whether these clinical observations are bortezomib-specific or  
1049 characteristic of the whole class of proteasome inhibitors is still open. Interestingly, cancer  
1050 cells with mutant *KRAS* shows selective addiction to proteasome activity (Steckel et al., 2012).  
1051 Indeed, in the case of oncogenic activation of specific axes, such as the Ras/Raf/ERK1/2 and  
1052 PI3K/Akt/mTOR pathways, there is an increased genome and proteome instability (Luo et al.,  
1053 2009) that is further increased by chemotherapy or radiotherapy. Such instability eventually  
1054 up-regulate the UPP system, making cells more refractory to proteasome inhibitors. Although  
1055 this scenario represents a difficult challenge in tumor eradication, it also opens the way to the  
1056 identification of new targets and new combination treatments specific for *KRAS* mutant  
1057 cancers, which are traditionally considered highly refractory to therapy.

#### 1058 **4.4. The role of an altered autophagy in the multidrug resistant phenotype**

1059 ALP is a self-catabolic process constituted by macroautophagy, microautophagy, and  
1060 chaperone-mediated autophagy. In macroautophagy, double membrane vesicles  
1061 (autophagosomes) formed by the activation of the autophagy related proteins (Atg) capture  
1062 lipids, proteins or organelles, and transfer them to lysosome for degradation (Klionsky et al.,  
1063 2016). ALP can also degrade ubiquitinated proteins via the action of microtubule-associated  
1064 histone deacetylase 6 (HDAC6) and p62/SQSTM1, which directly binds to ubiquitinated  
1065 protein aggregates (Gumeni and Trougakos, 2016). ALP is subjected to tight regulation by  
1066 several metabolic pathways. For instance, it is activated by AMPK and sirtuins, i.e. sensors of

1067 energy deprivation, and it is inhibited by insulin and downstream transducers such as mTOR,  
1068 that stimulate anabolic processes (Levine and Kroemer, 2008) and tumorigenesis (Hanahan and  
1069 Weinberg, 2011). Thus, an environment lacking oxygen and nutrients as is often seen in tumors  
1070 may favor cell survival through cytoprotective autophagy. Similarly, hypoxia being either  
1071 physiologically present in the bulk of solid tumors or induced by anti-angiogenic treatments  
1072 activates AMPK (Hu et al., 2012b) and consequently ALP.

1073 Although ALP activation may in some cases promotes cell death (Cui et al., 2014; Wei et al.,  
1074 2013) or anti-tumor immune responses (Janji et al., 2018; Jiang et al., 2019), in most tumors  
1075 the enhancement of ALP sustains the MDR phenotype beyond the ABC transporters, favoring  
1076 the recycling of building blocks, avoiding proteotoxic stress and sparing ATP. For instance, in  
1077 multiple myeloma ALP serves as a compensatory protein-clearance mechanism that eradicates  
1078 potentially toxic proteins, promoting resistance to proteasome inhibitors and tumor survival  
1079 (Driscoll and Chowdhury, 2012). Also, several anti-tumor therapies, including the DNA-  
1080 damaging chemotherapeutic temozolomide (He et al., 2019), cisplatin (Shen et al., 2015; Kim  
1081 and Kim, 2018), HDACs inhibitors (Mrakovcic et al., 2018) and radiotherapy (Chen et al.,  
1082 2010) induce a cytoprotective ALP (He et al., 2019), via the transcriptional induction of ALP  
1083 activators (Chen et al., 2011; Wang et al., 2018). In line with a cytoprotective role of autophagy,  
1084 its reduction enhances the toxic effects of cisplatin and 5-fluorouracil in esophageal and colon  
1085 cancer, respectively (Sui et al., 2015; Yu et al., 2014).

1086 As oncogenic TKRs activation drives malignant transformation and progression, TKIs become  
1087 a first-line treatment in several cancers; yet, TKIs' efficacy is also limited by the onset of  
1088 resistance which appears to be both ABC transporters-dependent or independent (Yamaoka et  
1089 al., 2018). ALP activation is one the mechanisms involved in the resistance to TKIs (Aveic and  
1090 Tonini, 2016). These "exposure/reaction mechanisms" are likely part of a conserved phenotype  
1091 of adaptation to stress that induce chemoresistance, whatever the drug is.

1092 For instance, the epidermal growth factor receptor (EGFR) inhibitors induce cytoprotective  
1093 autophagy (Cui et al., 2014), by reducing the Ras/Raf/MEK/ERK signaling in lung cancer  
1094 (Sooro et al., 2018), in metastatic colorectal cancer (Koustas et al., 2017), and in multidrug  
1095 resistant ovarian cancer (Ren et al., 2016). EGFR somatic mutations, which are found in many  
1096 patients with non-small-cell lung cancers, confer increased sensitivity to the EGFR inhibitors  
1097 gefitinib and erlotinib (Camidge et al., 2014). However, exposure to these EGFR-TKIs dose-  
1098 dependently increases ALP; this mechanism is at the basis of TKIs-resistance, as proved by the  
1099 finding that ALP inhibition in non-small-cell lung cancer cells enhanced the cytotoxic effect  
1100 of EGFR-TKIs (Sui et al., 2014).

1101 Also, resistance to afatinib in EGFR-mutated patients, to crizotinib in ALK break-positive  
1102 patients (van der Wekken et al., 2016), to BRAF inhibitors in BRAF-mutated melanoma (Liu  
1103 et al., 2018), and to mTOR inhibitors temsirolimus and everolimus in metastatic renal cell  
1104 carcinoma (Santoni et al., 2014) is associated with elevated ALP. These findings suggest that  
1105 ALP induction is a survival mechanism counteracting the cell death induced by anti-oncogenic  
1106 targeted therapies. Of note, this mechanism is shared by solid and hematological malignancies,  
1107 such as chronic myeloid leukemia where the introduction of imatinib is one of the most  
1108 successful examples of targeted therapy; yet, again, despite the success, imatinib-resistant  
1109 clones emerge. The resistance is (among others) mediated by increased cytoprotective ALP,  
1110 promoted by the activation of Unc-51 like autophagy activating kinase (ULK1) (Han et al.,  
1111 2019) and Atgs (Singh et al., 2018). The basis of resistance resides in the stem cell component  
1112 of chronic myeloid leukemia. Indeed, imatinib-non responders show an increased transcription  
1113 of autophagy-related genes such as Atg4b and Atg5 (Rothe et al., 2014), suggesting that the  
1114 ALP-dependent resistance is a precocious mechanism that is acquired during tumor evolution.

1115 These findings have triggered numerous ongoing preclinical and clinical studies based on  
1116 ALP inhibitors (e.g. chloroquine or hydroxychloroquine) to improve anti-cancer therapy, with

1117 encouraging partial responses and disease stabilization (Chude and Amaravadi, 2017).  
1118 Nevertheless, chloroquine and hydroxychloroquine do not specifically and exclusively  
1119 modulate autophagy and display several off-target effects resulting in substantial systemic  
1120 toxicities (Chude and Amaravadi, 2017). Thus, the screening for the identification of more  
1121 specific and less toxic ALP inhibitors is in progress. Currently, the main targets are ULK1/2,  
1122 Atg4b and the class III phosphoinositide 3-kinase VPS34 that inhibits ALP up-regulation in  
1123 response to chemotherapeutic agents (Limpert et al., 2018). In all cases, the main limitations  
1124 of these approaches is the lack of information about potential severe side-effects and toxicity  
1125 in healthy cells.

1126 It is generally accepted that ALP inhibitors facilitate the re-sensitization of resistant cells to  
1127 anticancer treatments. However, since cancer cells exhibit minimal basal autophagy levels  
1128 (Papanagnou et al., 2018), its inhibition will likely be of minimal utility as monotherapy. Thus  
1129 ALP becomes significant as an adaptive and cytoprotective response against targeted-therapies  
1130 that inhibit oncogenic pathways, like TKIs or agents increasing proteome instability (such as  
1131 proteasome inhibitors and chemotherapeutic drugs). Therefore, ALP inhibitors may have major  
1132 efficacy when combined with these anti-cancer treatments.

1133 An additional challenge is the development and validation of biomarkers able to predict  
1134 autophagy dependency and addiction in patients, as well as techniques able to monitor the  
1135 autophagic flux in humans. Given the high number of on-going phase I/II cancer clinical trials  
1136 involving chloroquine or hydroxychloroquine ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), the research interest in  
1137 the field remains vast.

1138

### 1139 **5. An altered lysosome homeostasis is involved in drug resistance**

1140 The ratio between intracellular and extracellular pH is critical in regulating drug influx and  
1141 efflux. The acidification of the intracellular milieu neutralizes the negative charge of

1142 phospholipids, decreases the superficial tension and determines an increased influx of charged  
1143 chemotherapeutic drugs, such as the weak bases (e.g. anthracyclines); consequently, the  
1144 intracellular alkalization produces the opposite effects (Omran et al., 2017). Moreover, the  
1145 intracellular alkalization generated by the anaerobic glycolytic metabolism may create a  
1146 slightly alkaline pH that is optimal for the efficient catalytic activity of Pgp (Äänismaa and  
1147 Seelig, 2007), increasing the efflux of several chemotherapeutic drugs.

1148 Therefore, lysosomes which are intracellular organelles whose activity is strictly pH-dependent  
1149 play a role in chemoresistance through multiple mechanisms (Zhitomirsky and Assaraf, 2016).  
1150 First, hydrophobic weak bases can easily diffuse within lysosomes, where they are protonated  
1151 and entrapped. This process involves anthracyclines (Zhitomirsky and Assaraf, 2017),  
1152 vinblastine (Yamagishi et al., 2013) and TKIs (Gotink et al., 2011; de Klerk et al., 2018). The  
1153 higher the difference between intracellular alkalization and extracellular acidification is, the  
1154 higher the pH gradient between cytosol and lysosomal lumen. This condition implies an  
1155 immediate protonation of the drugs entering lysosomes, increasing the sequestration and the  
1156 consequent development of resistance. Of note, the exposure to weak amines increases the  
1157 lysosomal biogenesis by promoting the nuclear translocation and transcriptional activation of  
1158 the transcription factor EB (TFEB). This mechanism is an additional protective strategy  
1159 adopted by cancer cells to increase resistance.

1160 Second, the lysosome membrane is rich of ABC transporters that actively accumulate drugs  
1161 within lysosomes against their concentration gradient. For instance, Pgp/ABCB1 (Yamagishi  
1162 et al., 2013) and ABCA3 (Chapuy et al., 2008) are localized on the lysosomal membrane, where  
1163 they contribute to doxorubicin resistance. Interestingly, the hypoxic environment of solid  
1164 tumors promotes the transcription of the *mdr1* gene via HIF-1 $\alpha$ , but also determines an  
1165 increased Pgp/ABCB1 recycling and localization on lysosomes (Al-Akra et al., 2018). These  
1166 two mechanisms contribute to chemoresistance, by increasing the drug efflux at the plasma-



1167 membrane as well as the drug sequestration within the lysosomes. Moreover, specific copper  
1168 transporters – such as the human copper transporter 1 (hCtr1), ATP7B and the copper  
1169 transporter 2 (Ctr2) – increase the lysosomal entry of metal-based drugs, such as platinum  
1170 derivatives, contributing to the resistance to this class of drugs (Zhitomirsky and Assaraf,  
1171 2016).

1172 Third, since lysosomes are subjected to a continuous cycles of fusion with the plasma-  
1173 membrane and exocytosis, they can extrude the accumulated drugs (Zhitomirsky and Assaraf,  
1174 2017). Of note, alterations in lysosomal pH homeostasis promote exocytosis. Such alterations  
1175 can be induced by inhibitors of lysosomal H<sup>+</sup>-ATPase (Sundler, 1997) or by the accumulation  
1176 of weak amines (Kazmi et al., 2013), as many chemotherapeutic drugs are. Moreover, TFEB,  
1177 the same transcription factor involved in lysosomal biogenesis, also promotes lysosome  
1178 exocytosis (Medina et al., 2011), thus providing an additional mechanism of resistance.

1179 Given the importance of lysosomes as mediators of MDR, these organelles have become  
1180 attractive targets in chemoresistant cells. For instance, thiosemicarbazone derivatives  
1181 (Seebacher et al., 2016; Al-akra et al., 2018) or tariquidar (Zhitomirsky et al., 2018) have been  
1182 proven to inhibit both plasma-membrane associated and lysosome-associated Pgp/ABCB1,  
1183 increasing drug intracellular accumulation and preventing its sequestration within lysosomes.

1184 Lysosomotropic agents, such as chloroquine and hydroxychloroquine successfully prevented  
1185 the accumulation of drugs within lysosomes by increasing the pH, but – despite the success at  
1186 preclinical level (de Klerk et al., 2018) – they had modest success in clinical setting because of  
1187 the high toxicity (Chude and Amaravadi, 2017). Recently, inhibitors of H<sup>+</sup>-ATPase have been  
1188 tested as an alternative strategy in increasing lysosomal pH (Taylor et al., 2015): these  
1189 inhibitors rescued the efficacy of doxorubicin, the frontline treatment in osteosarcoma, in  
1190 resistant tumors (Ferrari et al., 2013).

1191 Lysosomal disruption is another strategy currently being tested to achieve the double goal of  
1192 damaging resistant cells and releasing the drug from lysosomes. For instance, the strong  
1193 fluorophore imidazoacridinone is a weak amine and accumulates within the lysosome. It can  
1194 represent the lead compound for a photodynamic therapy that destroys lysosomes in multidrug  
1195 resistant non-small cell lung cancer and ovarian cancer cells, by increasing the release of  
1196 lysosomal enzymes and the intracellular amount of ROS (Adar et al., 2012). Amphyphilic co-  
1197 polymers, designed to be selectively accumulated within lysosomes, have achieved the same  
1198 results by increasing lysosomal permeabilization and preventing the lysosomal sequestration  
1199 of paclitaxel (Mostoufi et al., 2019). Using a similar approach, pH sensitive nano-bubbles  
1200 vectorized to lysosomes, releasing CO<sub>2</sub>, have been successfully tested against breast cancer  
1201 cells, as tools capable of killing cancer cells and restoring doxorubicin efficacy by disrupting  
1202 lysosomes (Yang et al., 2016).

1203 A potential threat of lysosome-targeting agents, as it happens for ALP inhibitors, is the  
1204 possibility of inducing undesired side-effects in non-transformed cells. However, tumor-  
1205 targeting strategies using conjugated pH-sensitive nanoparticles or photodynamic therapy may  
1206 increase the selectivity of lysosomotropic treatments in cancer cells. Moreover, since  
1207 chemotherapy itself often promotes lysosome biogenesis or exocytosis in resistant cells,  
1208 disrupting these circuitries may increase the efficacy against chemo-refractory tumors.

1209

## 1210 **6. Conclusions**

1211 ABC transporters are the phenotypic markers of a multidrug resistant phenotype. Despite the  
1212 high number of publications with preclinical models demonstrating their involvement in  
1213 chemoresistance, little evidence at clinical level indicate that they are the only factors  
1214 determining drug resistance (Fletcher et al., 2016). It is likely more appropriate to consider  
1215 ABC transporters as markers of a multi-stress resistant phenotype that allows cancer cells to

1216 survive in unfavorable conditions, such as hypoxia, nutrient deprivation, radiotherapy or  
1217 chemotherapy. Following the principle “What does not kill me, makes me stronger”, cancer  
1218 cells growing in stressful conditions elaborate multiple survival strategies (Hanahan and  
1219 Weinberg, 2011a). These adaptive processes unequivocally lead to the emergence of resistant  
1220 clones.

1221 In all cases, the higher the ability to adapt to changing and unfavorable conditions is, the higher  
1222 the resistance of cancer cells to different stressing stimuli. This dynamic plasticity is supported  
1223 not only by the increased expression of ABC transporters, but also by a wide reprogramming  
1224 of metabolism, proteostasis and functions of key intracellular organelles, such as mitochondria,  
1225 ER and lysosomes. This adaptive reprogramming not only increases the activity and/or  
1226 expression of ABC transporters but at the same time favor the activation or pro-survival/anti-  
1227 apoptotic pathways (Vidal et al., 2018; Valcarcel-jimenez et al., 2017; Maurel et al., 2015;  
1228 Zhitomirsky and Assaraf, 2016). Consequently, reprogrammed cells are more resistant to a  
1229 plethora of stressful conditions, determining a “multistress resistant phenotype” more than a  
1230 simple “chemoresistant phenotype”.

1231 The ability to shift between anaerobic and aerobic glucose metabolism, and obtain ATP supply  
1232 from both the metabolic processes (Icard et al., 2018), allows for an efficient activity of ABC  
1233 transporters, proteins degradation via proteasome and protective autophagy, either in response  
1234 to acute chemotherapeutic stress or after prolonged exposure to chemotherapy. Similarly, the  
1235 coordinated control of cytosolic and mitochondrial anti-oxidant and pro-oxidant enzymes,  
1236 allows cancer cells to be protected from acute oxidative damages induced by chemotherapy  
1237 and to maintain the ROS levels below a cytotoxic threshold. If ROS are below this “danger  
1238 threshold”, they act as signaling molecules, favoring cell survival and contributing to increase  
1239 the cross-resistance to environmental damaging agents (de Sá Junior et al., 2017; Moloney and  
1240 Cotter, 2018; Okon and Zou, 2015).

1241 Changes in mitochondria fusion/fission ratio and mitophagy (Cheng et al., 2016; Springer and  
1242 Macleod, 2016), in ER functions in response to stressful conditions (Hetz, 2012; Maurel et al.,  
1243 2015), in proteostasis and autophagic flux (Gumeni et al., 2017; He et al., 2019), in lysosome  
1244 endocytic/exocytic cycle (Zhitomirsky and Assaraf, 2016; Zhitomirsky and Assaraf, 2017) are  
1245 additional mechanisms that are easily reprogrammed by resistant cells in response to  
1246 chemotherapy. All these mechanisms support the multidrug resistant phenotype, either in ABC  
1247 transporter-dependent or independent ways.

1248 This broad spectrum of changes beyond ABC transporters may explain the failure of most  
1249 pharmacological inhibitors of the transporters that only target the “tip of the iceberg”, without  
1250 affecting the network of intracellular programs that provide favorable conditions for ABC  
1251 transporters efficiency. The importance of intracellular organelles as potential therapeutic  
1252 targets to reduce the expression/activity of ABC transporters and sensitize multidrug resistant  
1253 cells has emerged as a new promising strategy, exploiting organelles-vectorized  
1254 chemotherapeutic drugs (Buondonno et al., 2016; Buondonno et al., 2019) or nanoparticles  
1255 (Gao et al., 2019). Besides targeting organelles, the promising frontier refers to dissecting the  
1256 molecular circuitries that govern the plasticity of organelles’ functions, in order to enlarge the  
1257 number of multi-target agents being potentially effective against resistant cells. This strategy  
1258 will attenuate the resistance to chemotherapy and to other environmental stress conditions that  
1259 do not kill resistant clones, but promote their expansion.

1260 A second challenge is the fight against the high inter- and intra-tumor variability. Indeed, it is  
1261 common that the same altered function produces different effects in terms of  
1262 chemosensitization or chemoresistance in different tumors or in different patients with the same  
1263 tumor type. High-throughput and easy-to-use in the clinic assays able to measure key  
1264 parameters of altered metabolism and intracellular organelles function should be useful to  
1265 profile single patients’ specimens and to find a set of biomarkers potentially predictive of either

1266 chemosensitivity or chemoresistance. This approach may couple “precision –or personalized-  
1267 medicine” with “biochemistry/cell biology-driven medicine”, opening the way to develop new  
1268 multi-target tools reversing chemoresistance in a personalized fashion.

1269

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1279

### 1280 **Conflict of interest**

1281 None.

1282

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2645  
2646

2647 **Figure legends**

2648 **Figure 1. Multiple energetic and/or metabolic alterations contribute to multidrug**  
2649 **resistance.**

2650 Stressful conditions, including chemotherapy, nutrients deprivation or hypoxia, activate pro-  
2651 survival intracellular transducers (e.g. PI3K/Akt, ERK1/2/MAPK or sirtuins-dependent axes)  
2652 and downstream transcription factors (such as NF-kB, c-myc, PGC-1 $\alpha$ , c-jun, HIF-1 $\alpha$ , Nrf2,  
2653 FOXO3a) that promote resistance to stress. Most of these transducers and transcription factors  
2654 activate pro-survival and proliferative pathways including the induction of ABC transporters;  
2655 for instance, NF-kB, c-myc, HIF-1 $\alpha$  and FOXO3a upregulate Pgp/ABCB1 and Nrf2 upregulate  
2656 MRP1/ABCC1. Parallel to these effects, the activation of these pathways also causes an  
2657 extensive reprogramming of cellular energetic/metabolic functions. Specifically, the HIF-1 $\alpha$ ,  
2658 FOXO3a and PI3K/Akt/c-myc axes are known inducers of glycolysis, with a particularly strong  
2659 effect on HKII, PKM2 and LDH modules. PGC-1 $\alpha$  promotes mitochondrial biogenesis and  
2660 metabolism. In this way, glucose, that is taken up by GLUT proteins can be catabolized by  
2661 anaerobic glycolysis or TCA/OXPHOS. If glycolysis prevails, ATP is produced at low amounts  
2662 but at a fast rate. This feature, together with the intracellular alkalization that is promoted by  
2663 the export of lactate and H<sup>+</sup> via the MCT protein, supports the efficient catalytic activity of Pgp  
2664 for short periods. On the other hand, the ATP produced by mitochondrial TCA/OXPHOS is  
2665 generated at a slower rate but at a higher amount, and sustains the activity of ABC transporters  
2666 for longer periods. The simultaneous activity of glycolysis and TCA/OXPHOS, along with the  
2667 ability of cancer cells to shift among energetics pathways generates a metabolic phenotype able  
2668 to resist to both acute and prolonged chemotherapy, determining thus the onset and  
2669 maintenance of MDR. *Red arrows*: activation/induction processes.

2670

2671 **Figure 2. Cytosolic and mitochondrial oxidative-reductive pathways support multidrug**

2672 **resistance.**

2673 Exogenous (e.g. chemotherapy, radiotherapy, chronic inflammation; *violet box*) or endogenous  
2674 (e.g. OXPHOS/ATP synthesis uncoupling; *yellow box*) factors may increase intracellular ROS  
2675 to levels that cannot be buffered by anti-oxidant cellular defense systems. The unbuffered ROS  
2676 can amplify the damages on nuclear or mtDNA elicited by chemotherapy and/or radiotherapy,  
2677 leading to cell death and chemosensitization. By contrast, if cytosolic (PPP, xCT,  
2678 GR/GPX/GST systems, PRDX, Trx/TrxR systems, SOD1, catalase; *green box*) or  
2679 mitochondrial (SOD2, catalase, GST $\pi$ , IDH2; *orange box*) signaling pathways maintain the  
2680 ROS levels below the “stress threshold”, ROS are signaling molecules that activate pro-  
2681 survival pathways (PI3K/Akt axis, ERK1/2/MAPK axis, JNK) and transcription factors (NF-  
2682 kB, p53, HIF-1 $\alpha$ , Nrf2, FOXO3a) that up-regulate Pgp/ABCB1 and MRP1/ABCC1.  
2683 Consequently, low intracellular ROS levels induce cell survival and chemoresistance. The  
2684 balance between pro-oxidant stimuli and anti-oxidant defenses largely determines if ROS  
2685 levels remain are below or above the “stress threshold” and the consequent cell fate in response  
2686 to chemotherapy.

2687

2688 **Figure 3. A complex interplay among mitochondria dynamics (fission, fusion) and**  
2689 **mitophagy contributes to multidrug resistance.**

2690 Both fusion and fission of mitochondria support a multidrug resistant phenotype. On the one  
2691 hand, the prevalence of mitochondrial fusion, operated by Mfn1/2 and OPA1, increases the  
2692 production of ATP via OXPHOS and the ATP supply to ABC transporters; the amount of anti-  
2693 oxidant enzymes and mtDNA repairing enzymes, limiting the damages induced by  
2694 chemotherapy. On the other hand, cells with increased mitochondrial fission, driven by Drp1  
2695 under the control of Fis1, Mff and Mid, display chemoresistance, because of the lower  
2696 production of dangerous mtROS and the reduced diffusion of chemotherapy-related toxic

2697 substances to other mitochondria. Mitophagy, favored by the cooperation between PARK2,  
2698 PINK1 and BNIP3, becomes important in contributing to chemoresistance at advanced tumor  
2699 stages, when it decreases mtROS and toxins, and spares ATP. Depending on the tumor types  
2700 and stages, the cocktail of chemotherapeutic agents used and the cellular energetic needs; the  
2701 prevalence of fusion/fission dynamics or mitophagy may induce chemosensitivity or  
2702 chemoresistance. Chemoresistant clones have the highest ability of oscillating between these  
2703 three processes and exploiting them to resist chemotherapy-induced damage.

2704

2705 **Figure 4. Altered endoplasmic reticulum functions and autophagic/lysosomal flux favor**  
2706 **multidrug resistance.**

2707 Unfavorable environmental conditions, such as nutrients deprivation, hypoxia, radiotherapy  
2708 and chemotherapy, induce ER stress, i.e. a condition that increases the burden of unfolded  
2709 proteins within the ER lumen. Resistance to both ER stress and to chemotherapy often co-exist  
2710 in aggressive cancers. ER stress is sensed by GRP78 and specific sensors such as IRE1 $\alpha$ , PERK  
2711 and ATF6 that alter the global polypeptide translation rates, limiting the amount of unfolded  
2712 proteins. This mechanism reduces the accumulation of excessive levels of unfolded proteins  
2713 that could trigger an ER-dependent apoptosis in cancer cells with a defective ERAD/ERQC  
2714 system. Unfolded polypeptides are eliminated by the ubiquitination/proteasomal-degradation  
2715 and/or autophagy/lysosomal-degradation systems. The E1 ubiquitin-activating enzymes  
2716 activate IRE-1 $\alpha$ , PERK and ATF6/XBP1 that in turn may increase the proteasomal activities.  
2717 The elimination of unfolded proteins by this proteostatic network prevents the apoptosis  
2718 mediated by chemotherapeutic drugs, proteasome inhibitors and other targeted therapies.  
2719 Moreover, ER stress sensors – in particular PERK – activate multiple downstream transducers,  
2720 such as XBP1/HIF-1 $\alpha$ , c-jun, C/EBP- $\beta$  LIP that up-regulate Pgp/ABCB1 or Nrf2 that induces  
2721 MRP1/ABCC1. This mechanism provides an alternative mechanism that limits the intracellular

2722 accumulation of chemotherapeutic drugs promoting thus multidrug resistance.

2723

2724 **Figure 5. Alterations in the lysosome properties contribute to multidrug resistance.**

2725 Hypoxia and exposure to specific chemotherapeutic drugs, e.g. weak bases like anthracyclines

2726 (d), induce a lysosome-dependent chemoresistance. Specifically, hypoxia promotes anaerobic

2727 glycolysis that extrudes lactate and  $H^+$  via MCT, increasing the intracellular pH (pHi) and

2728 reducing the extracellular pH (pHe). This condition increases the catalytic efficiency of

2729 Pgp/ABCB1 and the sequestration of weak bases, including chemotherapeutic drugs, within

2730 the lysosomes. By inducing HIF-1 $\alpha$ , hypoxia induces the expression of Pgp/ABCB1 and its

2731 recycling to the lysosomal membrane, where the transporter contributes to sequestration of

2732 chemotherapeutic agents within the lumen. Moreover, exposure of cancer cells to

2733 chemotherapeutic drugs may activate TFEB, a transcription factor that increases lysosome

2734 biogenesis and exocytic processes; the net result being an increased drug sequestration coupled

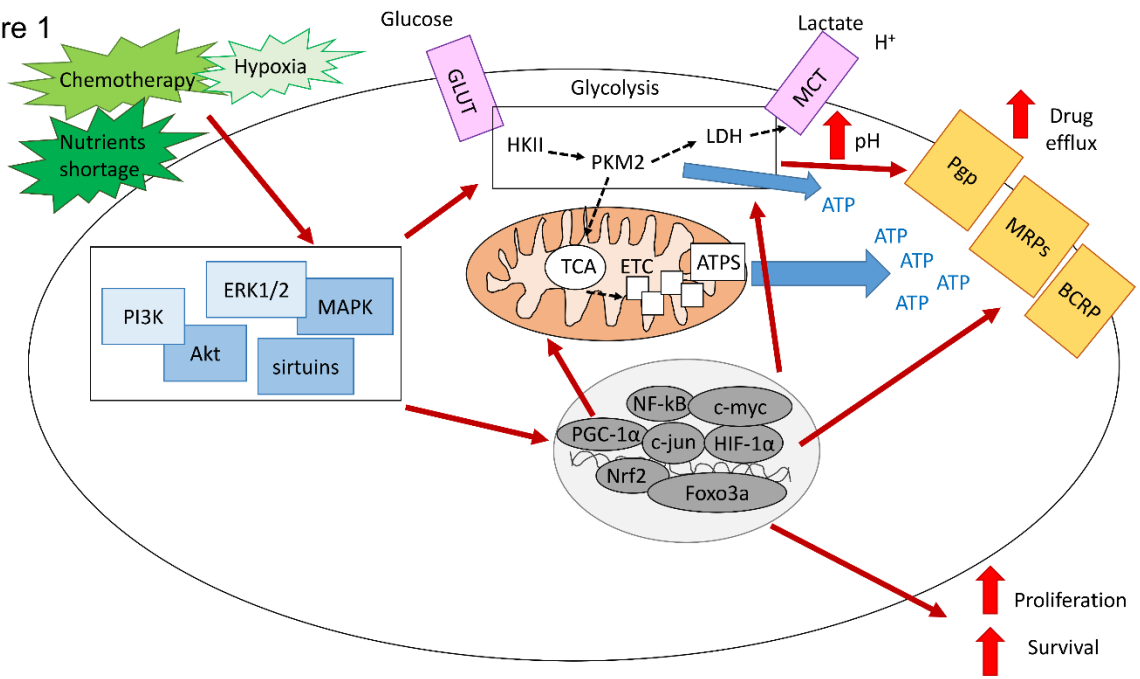
2735 to an increased drug extrusion via exocytosis. The combination of these events determines a

2736 strong drug resistant phenotype.

2737



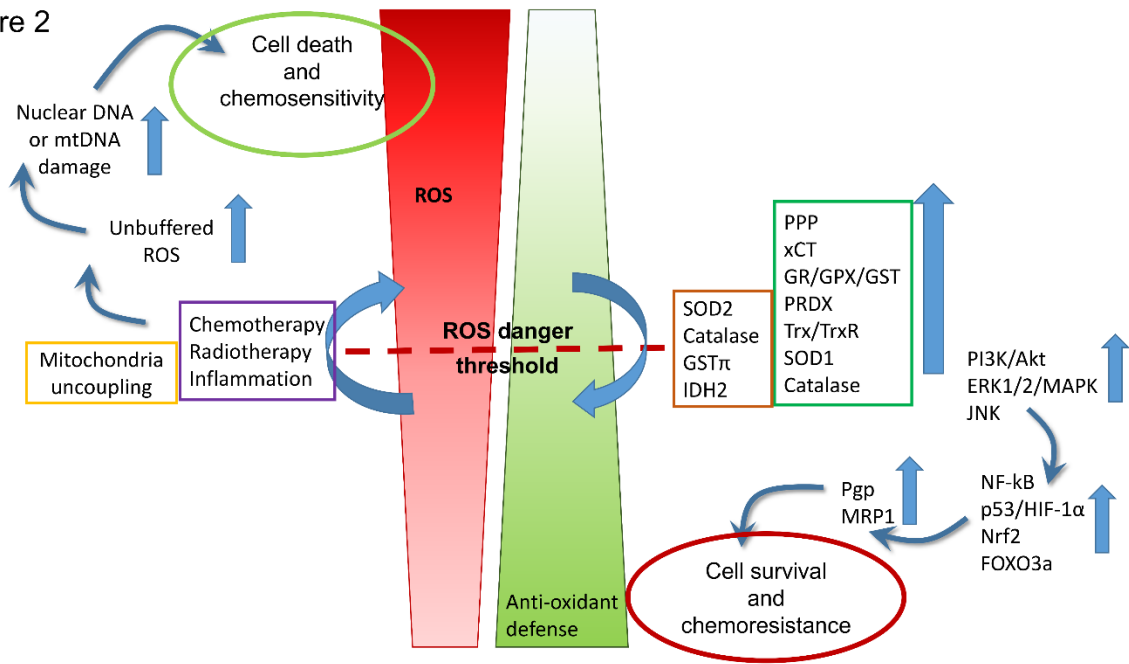
Figure 1



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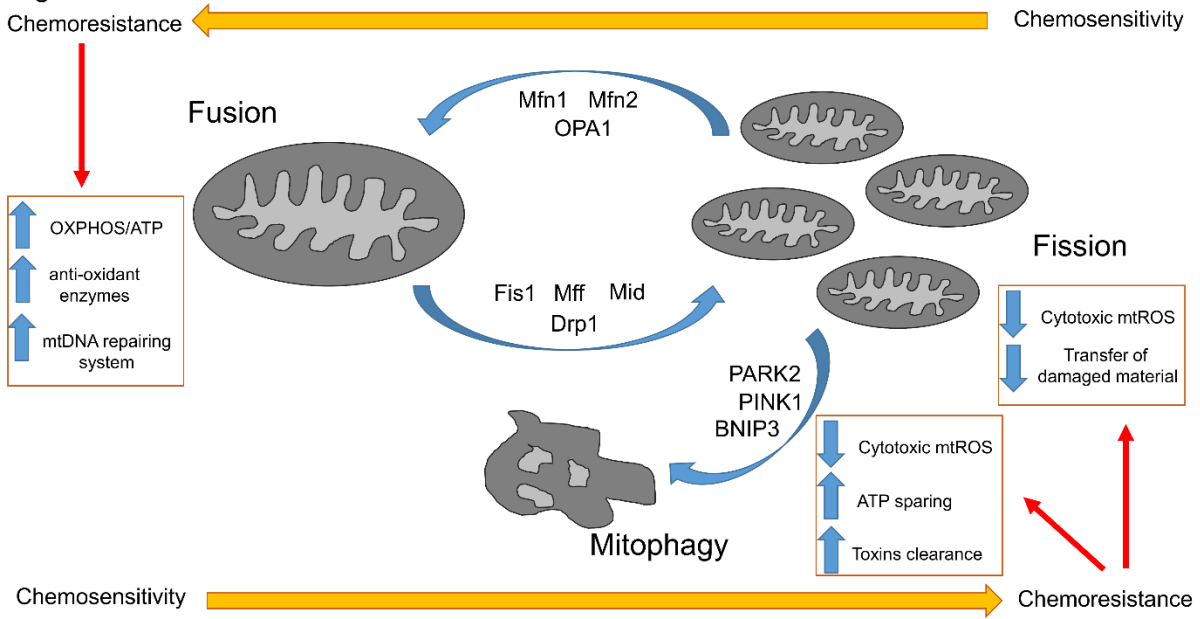
Figure 2



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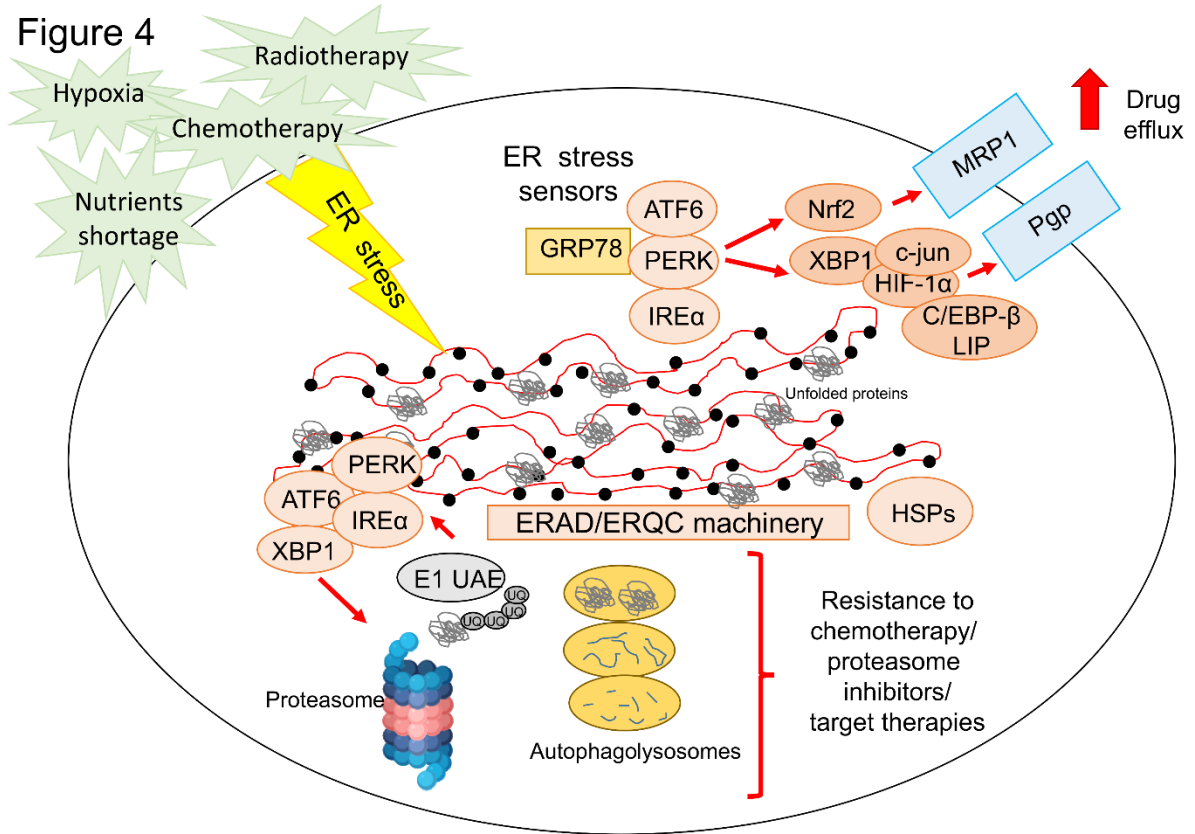
Figure 3



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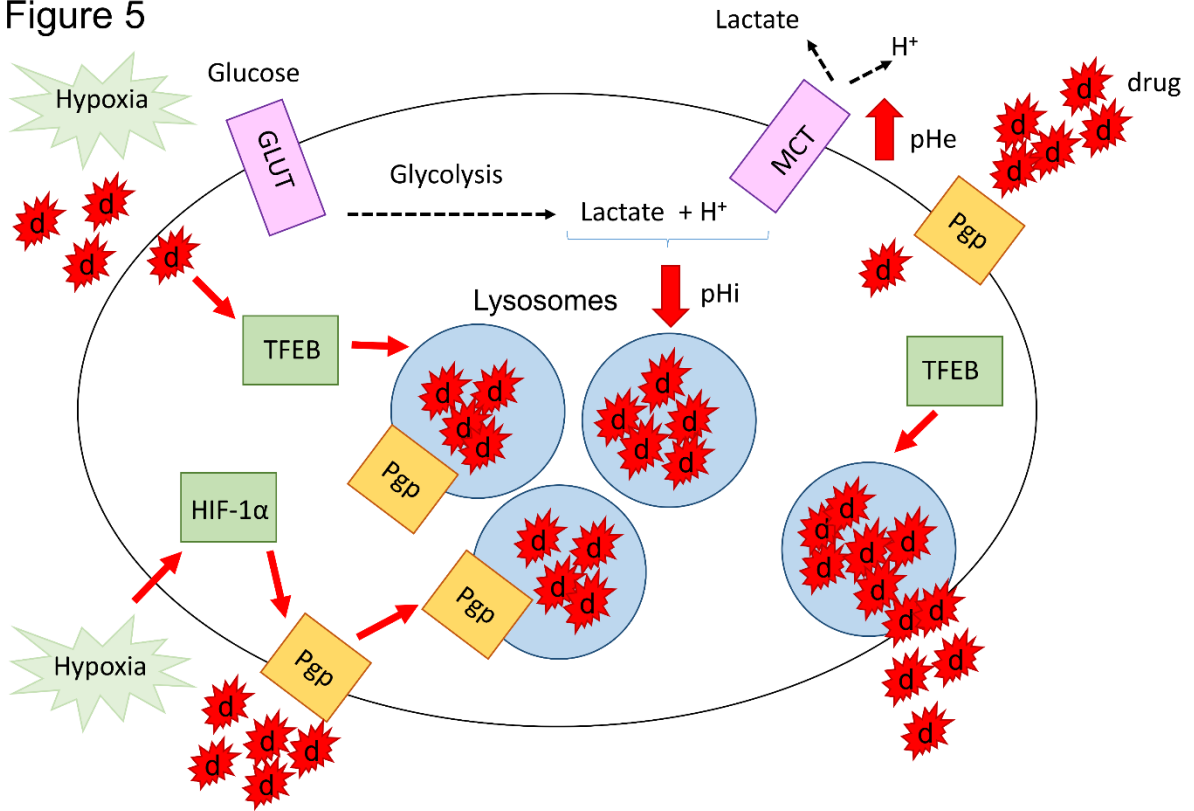
Figure 4



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2745

Figure 5



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