What sustains the multidrug resistance phenotype beyond ABC efflux transporters? Looking beyond the tip of the iceberg

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

Teodora Alexa-Stratulat[a,b], Milica Pešić[c], Ana Čipak Gašparović[d], Ioannis P. Trougakos[e], Chiara Riganti[f,g,*]

[a] Advanced Center for Research and Development in Experimental Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

[b] Department of Medical Oncology, Regional Institute of Oncology, Iasi, Romania

[c] Department of Neurobiology, Institute of Biological Research "Siniša Stanković", University of Belgrade, Serbia

[d] Division of Molecular Medicine, Institute Rudjer Bošković, Zagreb, Croatia

[e] Department of Cell Biology and Biophysics, Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece

[f] Department of Oncology, University of Torino, Italy

[g] Interdepartmental Center of Research in Molecular Biotechnology, University of Torino, Italy

*** Corresponding author at:** Department of Oncology, University of Torino, Italy. Email address: chiara.riganti@unito.it

Abstract

ATP Binding Cassette (ABC) transporters are considered a cause of multidrug resistance (MDR). However, their relevance in patients' chemoresistance and the long series of unsuccessful trials with ABC transporters inhibitors have pointed out that likely they are not the only cause of MDR. Several additional mechanisms evolve in cancer cells under sustained

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

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

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

Keywords

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

1. Introduction

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

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

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

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

2. A high metabolic plasticity favors multidrug resistance

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

Normal cells use the tricarboxylic acid (TCA) cycle for the catabolism of glucose, glutamine and fatty acids. In this process, oxidative phosphorylation (OXPHOS), which takes place within mitochondria, yields more than 30 ATPs from a single molecule of glucose (Vander Heiden et al., 2009). This process is enabled by the mitochondrial electron transport chain (ETC) that accepts electrons from reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) (Genova and Lenaz, 2014). Cancer cells need a continuous supply of nutrients (glucose, glutamine and essential amino acids) in order to obtain building blocks for macromolecules. Consequently, they use intermediates from both glycolysis and TCA cycle to synthetize nucleotides, proteins and lipids required for tumor growth (Anderson et al., 2018). Recent studies have shown that the benefit of aerobic glycolysis (the so-called "Warburg effect"), which is far less efficient than OXPHOS, is not merely limited to the production of ATP, but is linked to the generation of intermediates necessary for anabolic processes (Hosios et al., 2016; Lunt and Vander Heiden, 2011). In multidrug resistant cancer cells, the need for anabolic metabolites is coupled with the increased need of ATP supply from both glycolytic and OXPHOS origin (Zhou et al., 2012). Therefore, chemoresistant cells display a higher ability of exploiting these two energetic routes, resulting in increased ATP amounts that are available for ABC transporters.

2.1. Glycolysis-based metabolic reprogramming increases multidrug resistance

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

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

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

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

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

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

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

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

Nonetheless, the question of how the oscillations in blood glucose – naturally occurring in the mammalian tissues – impact on chemoresistance remains controversial. Paradoxically, lowering the supply of exogenous glucose, mimicking thus the physiological oscillations in glycemia, can both decrease or increase the ABC transporter functions in preclinical models. On the one hand, resistant cells adapt to glucose deprivation by using alternative fueling energy and increasing the expression of the glucose-regulated protein 78 (GRP78)-dependent anti-apoptotic pathways (Lee, 2007). On the other hand, lung and prostate cells with an acquired resistance to paclitaxel are more resistant in the presence of a cell culture medium enriched with glucose that fuels their main energy source, namely glycolysis (Aldonza et al., 2017). In these resistant cells the Forkhead box O3a (FOXO3a) transcription factor, which is a driver of

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

2.2 Oxidative phosphorylation plasticity mediates multidrug resistance

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

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

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

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

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

A high OXPHOS metabolism characterizes a subpopulation of the so-called "energetic cancer stem cells" (eCSC) in breast cancer (Fiorillo et al., 2019): these cells are resistant to classical chemotherapeutic drugs substrates of ABC transporters (Farnie et al., 2015), and are associated with clinical chemoresistance and poor outcome (Fiorillo et al., 2019). The OXPHOS inhibitor diphenyleneiodonium chloride effectively eradicates this population, reducing the probability of tumor relapse and progression. Also in patient-derived colonospheres the exposure to oxaliplatin and 5-fluorouracil increases mitochondrial biogenesis and boosts OXPHOS, by activating the histone deacetylase sirtuin-1 (SIRT1) and its substrate peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1α), a strong inducer of mitochondrial biogenesis (Vellinga et al., 2015). Preventing SIRT-1 activation re-sensitizes xenografts and colonospheres to chemotherapy (Vellinga et al., 2015), suggesting that preventing the increase

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

An active OXPHOS determines not only resistance to chemotherapy, but also to endocrine therapy (tamoxifen) in estrogen receptor-positive breast cancer cells. Indeed, tamoxifen induces oxidative stress associated with increased mitochondrial biogenesis and OXPHOS. Resistant cells have shown an increased expression of NAD(P)H dehydrogenase quinone 1 (NQO1) (Fiorillo et al., 2017), an enzyme that supplies reduced ubiquinone to the electron transport chain (Li et al., 2014). The NQO1 inhibitor dicoumarol reverses tamoxifen resistance (Fiorillo et al., 2017), by preventing an increase in the OXPHOS induced by tamoxifen as well as the emergence of resistant clones able to reprogram their metabolism boosting OXPHOS. Furthermore, an active OXPHOS, associated with an increased mitochondrial biogenesis, provides a metabolic phenotype that seems to be important for the acquisition of resistance to BRAF inhibitors such as vemurafemib (Zhang et al., 2016). Specifically, in melanoma cells with oncogenic activated BRAF, the treatment with vemurafemib increases OXPHOS by enhancing the PGC1α-mediated mitochondrial biogenesis (Haq et al., 2013). This process generates a population of ATP-rich and slow-cycling cells, which are resistant to mitogen activated protein kinase (MAPK) inhibitors.

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

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

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

2.3. Adaptation to hypoxia supports a multidrug resistant phenotype

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

Second, the limited number of nutrients and building blocks reduces tumor cell proliferation. Since chemotherapy is mainly active on highly proliferative cells, hypoxic quiescent cells are

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

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

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

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

Hypoxia and chemotherapy are not the only unique condition which increases HIF-1α. Curiously, mitochondrial ROS also stabilize HIF-1α. This mechanism is of paramount importance in triple negative breast cancer stem cells, where the pro-proliferative and anti-apoptotic myc-1 and myeloid cell leukemia-1 (MCL1) proteins favor the expansion of cancer stem cell-enriched populations that are highly chemoresistant and characterized by an increased OXPHOS-based metabolism (Lee et al., 2017). Preventing either HIF-1α stabilization or OXPHOS activity may have a particular therapeutic interest limiting the expansion of chemoresistant stem cells, i.e. the hardest tumor population to be eradicated. HIF-1α effects on chemoresistance are interconnected with other molecular circuitries. For instance, in colonospheres, the HIF-1α-activity is induced by the hypoxic environment and along with the transforming growth factor-β2 (TGF-β2) that is secreted by cancer associated fibroblasts, they both activate GLI2, a transcription factor that promotes stemness and chemoresistance to oxaliplatin and 5-fluorouracil, by increasing the ratio of anti-apoptotic/proapoptotic protein (Tang et al., 2018).

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

2.4. An altered cytosolic redox metabolism induces multidrug resistance

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

activator protein-1 (AP-1), NF-kB, HIF-1α and p53 (Görlach et al., 2015), thus providing multiple additional mechanisms for protection against chemotherapy.

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

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

G6PD, 6PGD and TKT, a low expression of PRDX2 and NADPH regenerating enzymes (e.g. G6PD, 6PGD and isocitrate dehydrogenase 1 - IDH1), but surprisingly they have high levels of GSH (Lopes-Rodrigues et al., 2017). In this case, the high levels of GSH are due to the increased metabolism of methionine that supplies cysteine residues necessary for *de novo* GSH synthesis (García-Giménez et al., 2017). This phenotype also provides higher amounts of methyl groups and supports the increased ability of DNA methylation (Arrigoni et al., 2016), also implying that epigenetic changes are likely involved in the acquisition of chemoresistance. These experimental evidence suggest that multiple mechanisms, either PPP-dependent or PPP-independent, may increase the levels of GSH and favor a chemoresistant phenotype.

Disrupting the balance between the PPP rate, GSH levels and ROS levels may provide new chemosensitizing strategies. For instance, the therapeutic success of purine and pyrimidine nucleotide/nucleoside analogs is hampered in cells with an active *de novo* synthesis of nucleotides (Shelton et al., 2016) that relies on PPP. Inhibiting PPP or GSH opens the possibility for synergistic intervention with the existing anti-metabolite agents. Of note, a quite unexplored purine nucleoside analog, namely sulfinosine, sensitizes MDR cancer cells to doxorubicin by lowering the GSH levels and exerting a pro-oxidant activity, coupled with the decreased expression of Pgp/ABCB1 mediated by HIF-1α (Dačević et al., 2013).

Inhibiting G6PD not only sensitizes cells to chemotherapy but also to targeted therapies: for instance in triple wild type (KRAS/NRAS/BRAF) multiple myeloma cells, the G6PD inhibitor 6-aminonicotinamide (6AN) significantly increases the anti-proliferative efficacy of the EGFR inhibitors gefitinib and afatinib (Chen et al., 2015). The mechanism relies on the increase of ROS, because the sensitizing effects of 6AN are lost when cells are supplemented with NADPH. Similarly, the natural glucoside polydatin, a G6PD inhibitor, is synergic with the EGFR inhibitor lapatinib in MCF-7 cells, by inducing oxidative stress, activating autophagic

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

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

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

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

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

bypassing the "danger threshold". For instance, ferrocene-quinidine epimers exert a strong pro-oxidant activity and induce a strong mitochondrial damage in MDR cancer cells (Podolski-Renić et al., 2017). Importantly, these compounds are more effective, alone or in combination with paclitaxel, against non-small cell carcinoma and colorectal carcinoma chemoresistant cells than against their sensitive counterparts (Podolski-Renić et al., 2017), likely because of the different redox status of resistant cells. A similar preferential cytotoxicity towards MDR cancer cells is displayed by pro-oxidant derivatives of natural occurring compounds, such as avarone, tert-butylquinone (Jeremić et al., 2016) and protoflavone (Stanković et al., 2015).

Having constantly higher levels of ROS and anti-oxidant enzymes compared to chemosensitive cells, some MDR cells are able to maintain a constant control of intracellular ROS exploiting them as pro-survival and stress-resistant signal molecules. On the other hand, this condition represents an instable equilibrium: strong pro-oxidant agents may turn the positive role of ROS into a negative role, explaining the peculiar sensitivity of MDR cells to direct killing (Pluchino et al., 2012) and chemosensitizing effects of pro-oxidant agents.

3. Changes in mitochondria functions support multidrug resistance

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.2. Altered mitophagy and multidrug resistance

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

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

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

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

For these reasons, inhibiting mitophagy may restore chemosensitivity and several studies have assessed the effect of combining classic chemotherapeutic agents with mitophagy inhibitors. The mitochondrial division inhibitor 1 (Mdivi-1) is a Drp1 inhibitor that prevents mitophagy in a fission-dependent manner (Li et al., 2017). Mdivi-1 re-sensitizes chemoresistant cancer cells (Kong et al., 2015), restoring the sensitivity to cisplatin in resistant cholangiocarcinoma cell lines (Qian et al., 2014). Of note, the Mvidi1-cisplatin combination preferentially affects cancer cells over non-transformed cells (Tusskorn et al., 2019), likely as a consequence of a

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

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

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

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

3.3. Altered redox mitochondrial metabolism in multidrug resistant cells

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

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

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

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

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

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

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

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

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

4. Changes in endoplasmic reticulum-dependent functions and proteostasis support multidrug resistance

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

The ER is the site where nascent proteins are folded and subjected to post-translational modifications before being delivered to the Golgi apparatus for further modifications and to their final destination. Plasma-membrane associated proteins, including ABC transporters, follow this pathway (Trowitzsch and Tampé, 2018). Each step of proteins modification is tightly controlled by the ER-associated protein degradation/ER-quality control (ERAD/ERQC) system, a complex of ER-associated proteins that sort the properly folded proteins and target for degradation the unfolded/misfolded polypeptides (Printsev et al., 2017; Hano et al., 2018). Hypoxia, nutrient deprivation, radiotherapy or chemotherapy – a range of conditions often experimented by cancer cells – induce the accumulation of unfolded/misfolded proteins within the ER lumen. This condition is sensed by GRP78 that is strictly associated to ERAD/ERQC proteins and activates three ER stress sensors, namely inositol-requiring protein 1α (IRE1α), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6). By recruiting different downstream transducers, IRE1α, PERK and ATF6 mount the so-called unfolded protein response (UPR) that promotes cell survival if the ER stress is reversible or short, but induces cell death in the case of prolonged and uncontrolled ER stress (Hetz, 2012; Maurel et al., 2015).

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

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

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

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

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

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

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

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

In contrast with the previous evidence, the activation of GRP78 by betulinic acid triggers the activation of the PERK/CCAAT/enhancer-binding protein homologous protein (CHOP) apoptotic pathway in breast cancer cells. This mechanisms restores the sensitivity to taxol (Cai et al., 2018). The presence of contrasting evidence on the role of ER stress as inducer or inhibitor of chemoresistance may be explained by the different stimuli that specifically activate one ER-downstream signaling over the others, by the duration of the ER stressing conditions (e.g. acute *vs*. prolonged ER stress) as well as by the pattern of ER-dependent transducers that may highly vary in different tumor types. For instance, in resistant pancreatic cells, gemcitabine resistance is associated with up-regulation of ATF4 and CHOP that exerts anti-apoptotic functions in these cells, as well as the accumulation of the phospho(Ser51)-eukariotic initiating factor 2α (eIF2α) that reduces protein synthesis. This mechanism prevents the accumulation of unfolded polypeptides and ER stress-mediated cell death. By contrast, ATF4 silencing – i.e. the deprivation of a classical ER stress sensor – restores the UPR response and the sensitivity to gemcitabine in this cancer type (Palam et al., 2015).

Therefore, it is hard to predict a common biological phenotype linking ER dysfunctions to chemoresistance. For example, a proteomic analysis of non-small cell lung cancer cells showed that resistance to cisplatin is associated with the overexpression of IRE1α, disulfide isomerase PDIA4 and PDIA6, and to the down-regulation of GRP78, PERK and ATF6 (Tufo et al., 2014), while in other tumors chemoresistance is associated to a completely different profile of ER-related proteins. Only an in-depth molecular characterization of tumor subtypes may identify

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

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

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

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

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

In a curious anti-parallelism with the mitochondrial phenotype of chemoresistant cells, the increase of resistance is associated with a progressive increase in the expression of mitochondrial energetic metabolism-related genes and with a progressive decrease in the expression of ERAD/ERQC genes. In particular, osteosarcoma chemoresistant cells have a defective ERAD/ERQC system that make them constantly subjected to a chronic ER stress. This situation promotes the basal up-regulation of pro-survival pathways that contribute to resistance to chemotherapy (Buondonno et al., 2019). However, this ER stress response represents an unstable equilibrium. Pharmacological approaches, based on disulfide-releasing doxorubicin vectorized within the ER, disrupt the defective ERAD/ERQC system of resistant cells, increasing the amount of unfolded and ubiquitinated proteins within the ER, and triggering an ER-dependent apoptosis (Buondonno et al., 2019). Such a response is less pronounced in sensitive cells that possess a functioning ERAD/ERQC system, revealing an Achille's heel of resistant cells. These data are supported by a large phenotypic and genotypic analysis of chemoresistant multiple myeloma cells present in patients with minimal residual disease, showing that chemoresistant clones – responsible of tumor relapse and poor outcome – are characterized by an intense down-regulation of ERAD/ERQC genes (Paiva et al., 2019). Among the proteins that require proper folding within the ER there is the Pgp/ABCB1. Therefore, inhibiting the ERAD/ERQC system in resistant cells inevitably determines the misfolding and ubiquitination of this ABC transporter, providing an additional mechanism of chemosensitization (Buondonno et al., 2019). In agreement with this finding, Ag-nanoparticles inducing ER stress overcome drug resistance by decreasing the Pgp/ABCB1 expression

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

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

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

Besides its role in protein folding and inducing UPR, ER has revealed an unexpected role as drug sequestration organelle. Specifically, the 3-β-hydroxysteroid-Δ8,Δ7-isomerase/emopamil-binding protein (EBP), an ER-associated enzyme physiologically involved in sterol biosynthesis, has recently displayed the properties of a multidrug binding protein, able to capture multiple anionic drugs in its central cavity (Long et al., 2019). This finding confirms that, besides plasma-membrane associated ABC transporters, other intracellular organelles and associated enzymes also strongly contribute to MDR.

4.2. The response to proteotoxic stresses in chemoresistant cells

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

proteome instability). PN addresses the triage decision of *fold*, *hold*, or *degrade* (Sala et al., 2017; Sklirou et al., 2018). The key functional modules of the PN are the cytosolic and ER sites of proteins synthesis, along with the machineries of proteins sorting and trafficking, the UPR machinery of the ER (UPR^{ER}) and mitochondria (UPR^{MT}), the intra- and extra-cellular network of molecular chaperones (also known as Heat Shock Proteins, HSPs), the compartmentalized (e.g. nuclear, cytosolic or mitochondrial) proteases, and the highly regulated degradation machineries of the ubiquitin-proteasome (UPP) and autophagy-lysosome (ALP) systems (Kaushik and Cuervo, 2015; Sklirou et al., 2018). Misfolded polypeptides tagged with ubiquitin are mainly degraded by the UPP system (Tsakiri and Trougakos, 2015). ALP activation prevails when the UPP system is overwhelmed; the HSP repairing/folding system fails resulting in the accumulation of protein aggregates or upon the extensive deterioration of cellular organelles (Tsakiri and Trougakos, 2015). Autophagy starts with autophagosome formation, followed by its fusion with lysosomes for degradation of the cargo (Klionsky et al., 2016). Moreover, proteotoxic stress regulates the activity of eIF2α, which triggers a general inhibition of protein synthesis triggers and cell cycle arrest (McConkey, 2017).

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

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

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

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

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

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

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

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

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

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

UPP is composed of ubiquitin-conjugating enzymes and 26S proteasome; the latter consists of a catalytic 20S core particle bound to a 19S regulatory particle (Tsakiri and Trougakos, 2015). The 20S particle is composed of four stacked heptameric rings that form a barrel-like structure. The caspase-, trypsin- and chymotrypsin-like peptidase activities are located at the β1, β2, and β5 proteasomal subunits, respectively. The 19S particle is involved in substrate recognition, de-ubiquitination, unfolding and translocation into the 20S portion (Tsakiri and Trougakos, 2015). The catalytic activity of the proteasome is crucial in protein quality control, as unfolded, misfolded, or non-functional newly synthesized polypeptides are targeted to cytosolic or ER-bound proteasomes (ERAD; see above) for degradation (Qi et al., 2017). Proteasomes are also found in the nucleus and in the OMM, where during activation of the UPR^{MT} they mediate the so-called outer mitochondrial membrane-associated degradation (OMMAD). OMMAD degrades damaged proteins from OMM and matrix, controlling mitochondrial proteostasis (Baker et al., 2011). Moreover, UPP degrades mitochondrial proteins involved in fusion and

fission (Wang et al., 2011; Wiedemann et al., 2013), regulating mitochondria dynamics. Since both mitochondrial fusion and fission are important in determining chemoresistance, OMMAD provides the functional linkage between altered mitostasis, altered proteostasis and MDR.

Proteasomal activity is significantly induced during sustained proteotoxic stress, e.g. during tumorigenesis or exposure to chemotherapy (Sklirou et al., 2018). Similarly to the non-oncogenic addiction to proteostatic systems, cells exposed to chemotherapeutic drugs become dependent on an efficient proteasome activity for their survival. Consistently, proteasome inhibitors were turned out to be very effective drugs against specific malignancies, such as multiple myeloma (Manasanch and Orlowski, 2017). Proteasome inhibitors of the first (bortezomib) or second (carfilzomib) generation, along with the orally administered novel agents (ixazomib), take advantage of the heavy reliance of myeloma cells on the 26S proteasome for the degradation of excessive or misfolded monoclonal immunoglobulins and/or free light chains produced (Bianchi and Anderson, 2019; Farrell and Reagan, 2018).

Nonetheless, as for most other tumor therapies, resistance to proteasome inhibitors is often observed in patients (Robak et al., 2018). Known mechanisms of resistance include the increased levels of proteasomes in tumor cells, the sole overexpression of the β5 proteasomal subunit PSMβ5 (Balsas et al., 2012), or even mutations in proteasomal subunits that make cells insensitive to the inhibitors (Robak et al., 2018). Reportedly, resistance to proteasome inhibitors may also relate to the increased UPR that overwhelms the UPP capacity (Hetz, 2012; Maurel et al., 2015), to the accumulation of aggresomes that up-regulate protective autophagic responses (see below), to the aberrant activation of pro-survival signaling pathways (Niewerth et al., 2015), to the defective apoptosis, senescence and DNA repair mechanisms (Dolloff, 2015; Wallington-Beddoe et al., 2018), and to the induction of Pgp/ABCB1 (Abraham et al., 2015). Interestingly, at a systemic level resistance to proteasome inhibitors may be also caused

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

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

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

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

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

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

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

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

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

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

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

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

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

5. An altered lysosome homeostasis is involved in drug resistance

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

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

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

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

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

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

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

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

Lysosomal disruption is another strategy currently being tested to achieve the double goal of damaging resistant cells and releasing the drug from lysosomes. For instance, the strong fluorophore imidazoacridinone is a weak amine and accumulates within the lysosome. It can represent the lead compound for a photodynamic therapy that destroys lysosomes in multidrug resistant non-small cell lung cancer and ovarian cancer cells, by increasing the release of lysosomal enzymes and the intracellular amount of ROS (Adar et al., 2012). Amphyphilic co-polymers, designed to be selectively accumulated within lysosomes, have achieved the same results by increasing lysosomal permeabilization and preventing the lysosomal sequestration of paclitaxel (Mostoufi et al., 2019). Using a similar approach, pH sensitive nano-bubbles vectorized to lysosomes, releasing CO_2, have been successfully tested against breast cancer cells, as tools capable of killing cancer cells and restoring doxorubicin efficacy by disrupting lysosomes (Yang et al., 2016).

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

6. Conclusions

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

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

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

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

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

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

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

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

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Conflict of interest

None.

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Figure legends

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

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

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

resistance.

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

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

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

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

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

Unfavorable environmental conditions, such as nutrients deprivation, hypoxia, radiotherapy and chemotherapy, induce ER stress, i.e. a condition that increases the burden of unfolded proteins within the ER lumen. Resistance to both ER stress and to chemotherapy often co-exist in aggressive cancers. ER stress is sensed by GRP78 and specific sensors such as IRE1α, PERK and ATF6 that alter the global polypeptide translation rates, limiting the amount of unfolded proteins. This mechanism reduces the accumulation of excessive levels of unfolded proteins that could trigger an ER-dependent apoptosis in cancer cells with a defective ERAD/ERQC system. Unfolded polypeptides are eliminated by the ubiquitination/proteasomal-degradation and/or autophagy/lysosomal-degradation systems. The E1 ubiquitin-activating enzymes activate IRE-1α, PERK and ATF6/XBP1 that in turn may increase the proteasomal activities. The elimination of unfolded proteins by this proteostatic network prevents the apoptosis mediated by chemotherapeutic drugs, proteasome inhibitors and other targeted therapies. Moreover, ER stress sensors – in particular PERK – activate multiple downstream transducers, such as XBP1/HIF-1α, c-jun, C/EBP-β LIP that up-regulate Pgp/ABCB1 or Nrf2 that induces MRP1/ABCC1. This mechanism provides an alternative mechanism that limits the intracellular

accumulation of chemotherapeutic drugs promoting thus multidrug resistance.

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

Hypoxia and exposure to specific chemotherapeutic drugs, e.g. weak bases like anthracyclines (**d**), induce a lysosome-dependent chemoresistance. Specifically, hypoxia promotes anaerobic glycolysis that extrudes lactate and H^+ via MCT, increasing the intracellular pH (pHi) and reducing the extracellular pH (pHe). This condition increases the catalytic efficiency of Pgp/ABCB1 and the sequestration of weak bases, including chemotherapeutic drugs, within the lysosomes. By inducing HIF-1α, hypoxia induces the expression of Pgp/ABCB1 and its recycling to the lysosomal membrane, where the transporter contributes to sequestration of chemotherapeutic agents within the lumen. Moreover, exposure of cancer cells to chemotherapeutic drugs may activate TFEB, a transcription factor that increases lysosome biogenesis and exocytic processes; the net result being an increased drug sequestration coupled to an increased drug extrusion via exocytosis. The combination of these events determines a strong drug resistant phenotype.

Figure 1

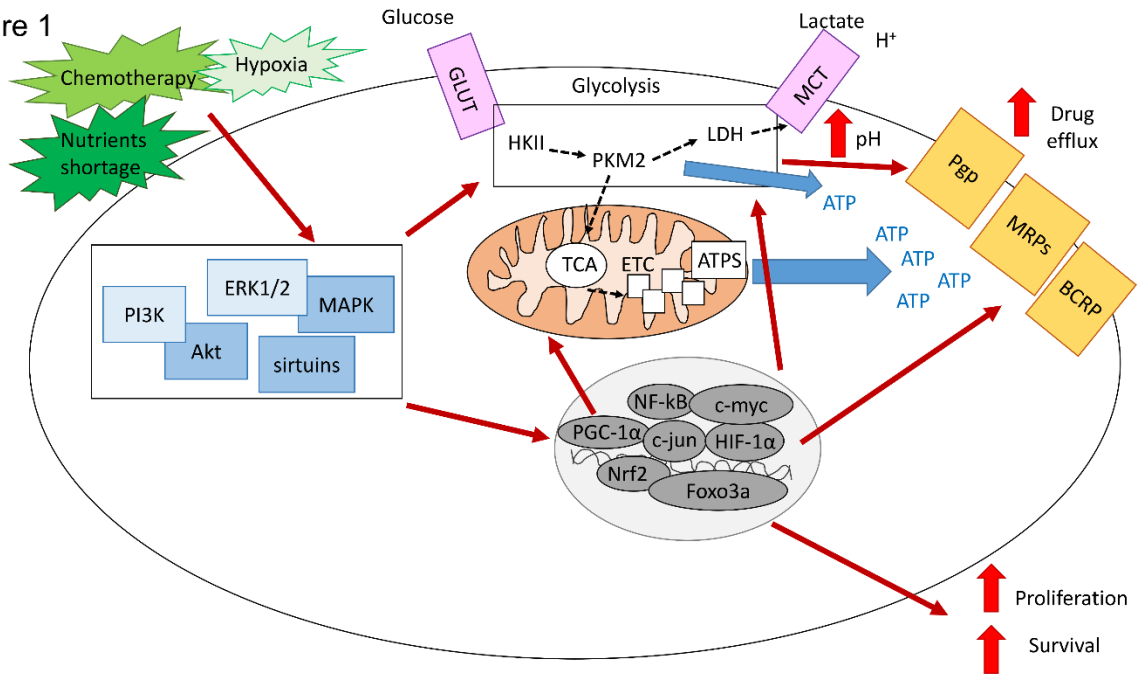

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Figure 2

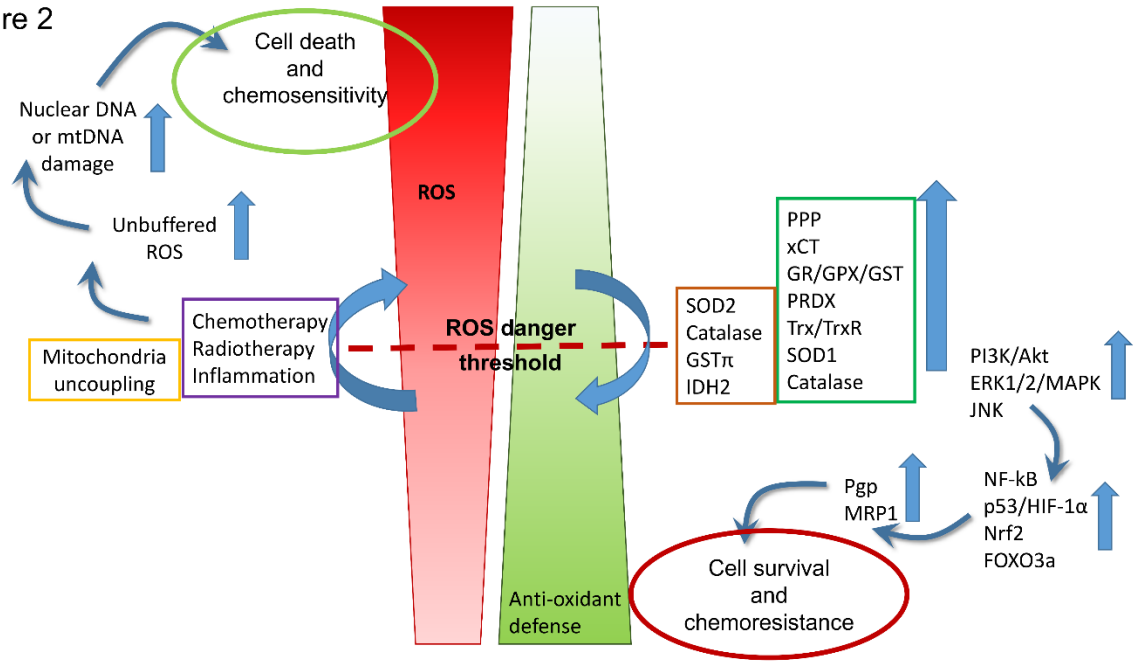

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Figure 3

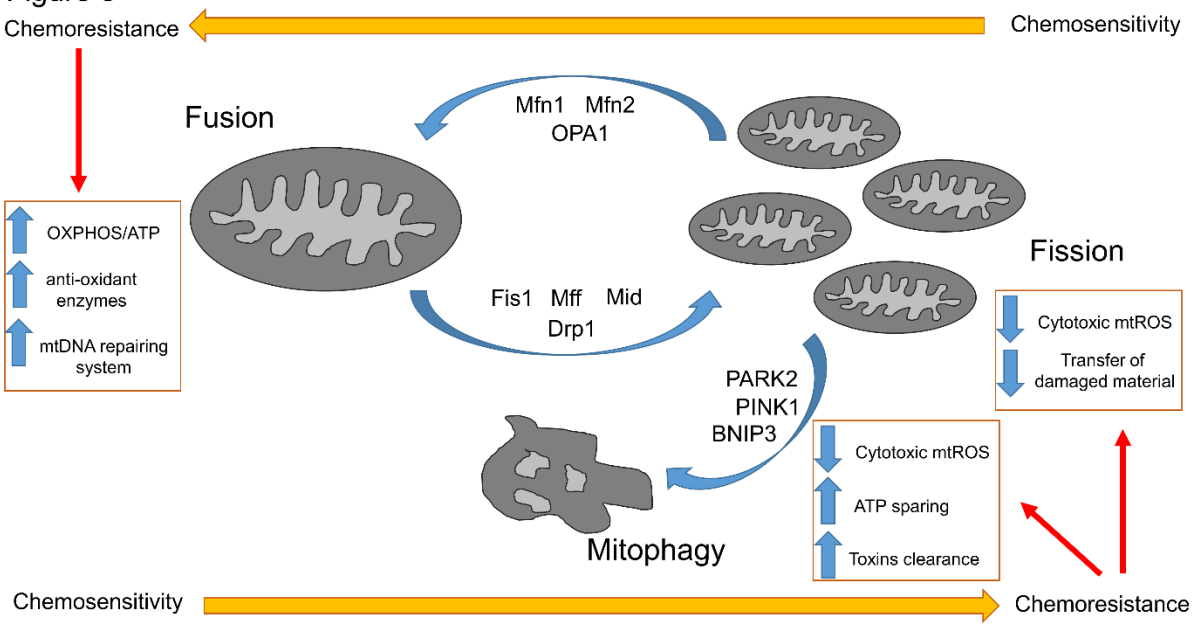

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Figure 4

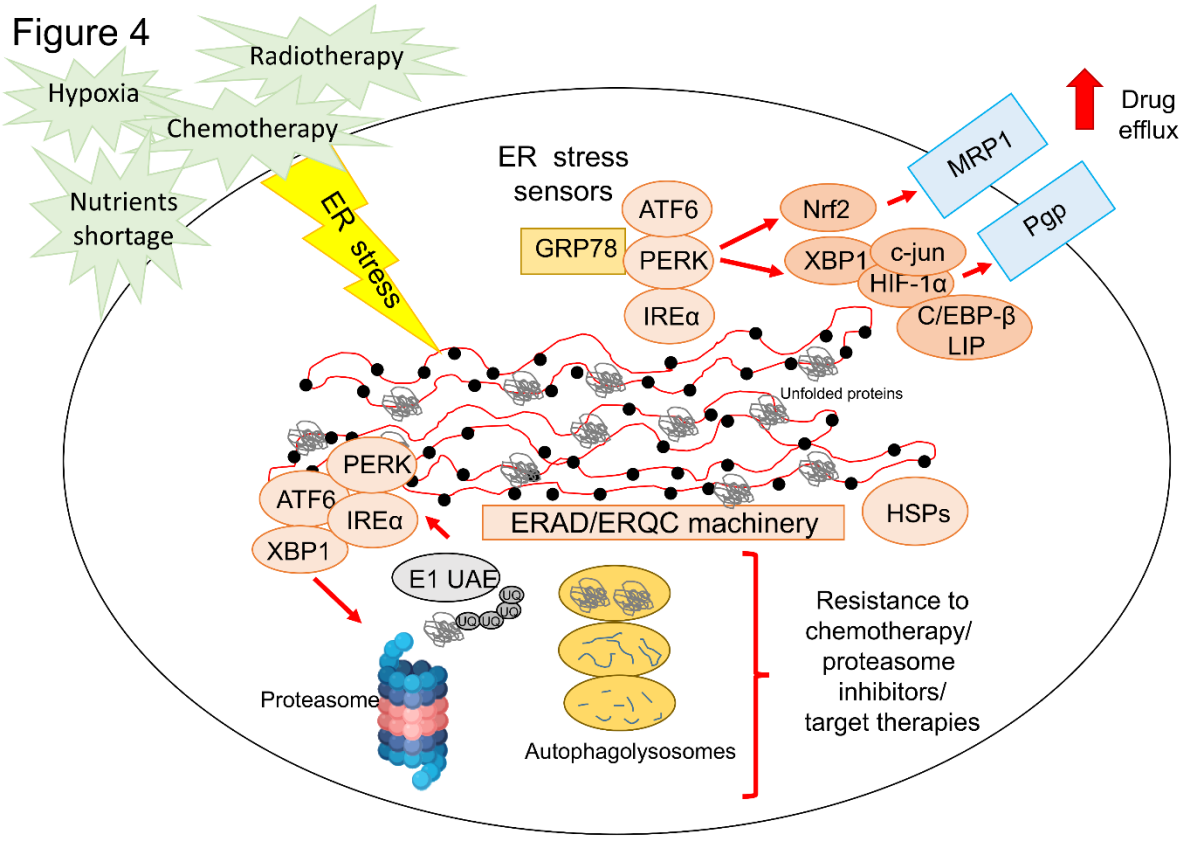

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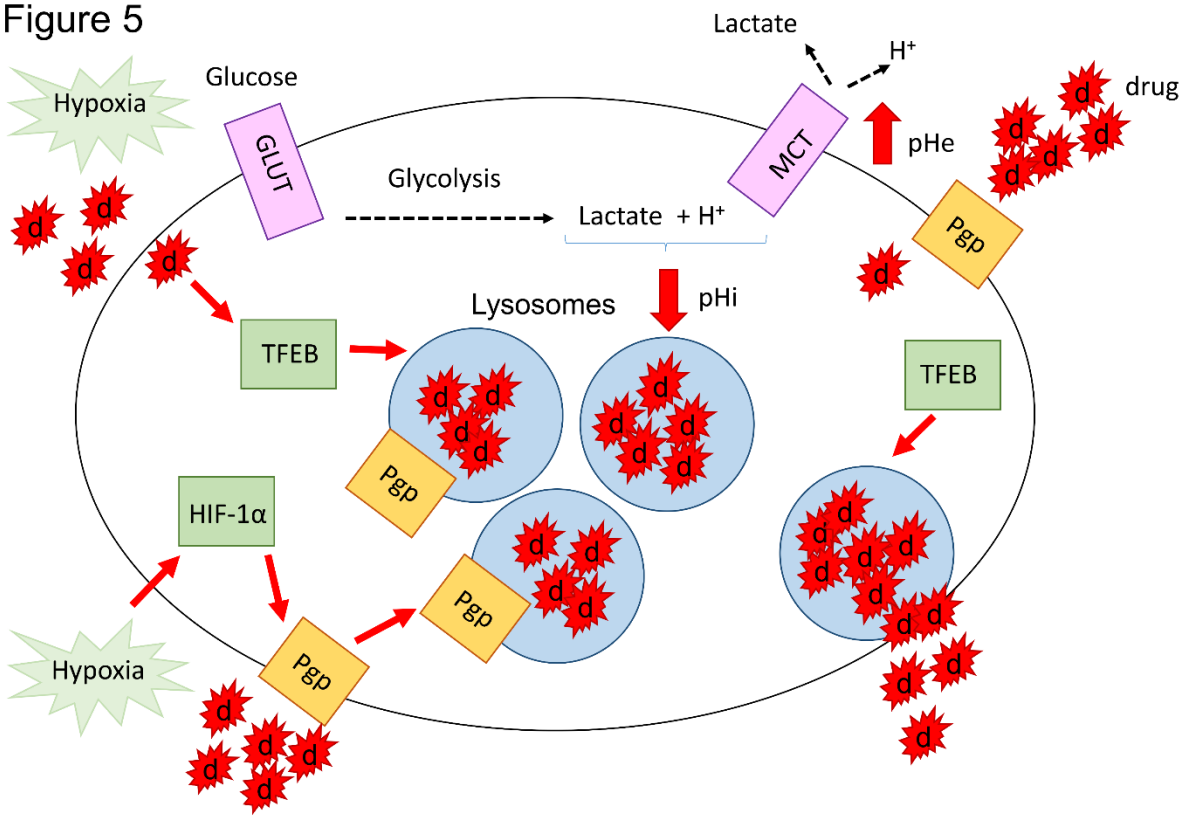
Figure 5



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