Chapter 2

Mitochondrial Dysfunction on the Toxic Effects of Anticancer Agents— From Lab Bench to Bedside

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http://dx.doi.org/10.5772/59488

1. Introduction

Cancer will become a major cause of morbidity and mortality in the next decades. It is estimated that the global cancer rate may increase by 75 %, with predicted 22.2 million new cases by 2030 compared with 12.7 million cases in 2008 [1]. The scientific community has made tremendous efforts to develop new therapies to deal effectively with this growing problem. As the recent advances in cancer therapy are improving the cancer patient survival, the toxic effects promoted by anticancer agents have a higher potential impact on long-term outcomes.

Anticancer agents are known to cause severe toxic effects that should be anticipated and carefully monitored. Therapeutic regimens targeting the cell cycle also affect the proliferation of normal cells, such as blood cells in the bone marrow, cells in the digestive tract and hair follicles, resulting in neutropenia, hair loss, and gut toxicity. The side effects observed are dependent on the type of therapy, but they are generally reversible and disappear after the end of the treatment. However, some anticancer agents may also affect, sometimes in a permanent manner, the function of vital organs, such as the heart, kidney, liver and the nervous system. Some of these effects may develop during or shortly after treatment, or may only become apparent a long period after completion of the treatment; if this delay is long enough, it may correspond to the time of progression free survival and affect the benefit-risk balance [2, 3].

Both the liver and kidneys are vulnerable to the toxic effects of cancer therapy and also to the direct impact of cancer itself. The liver has a great capacity to resist injury and to regenerate, but this capacity also makes it susceptible to anticancer drugs toxicity [2]. Indeed, the liver

injury induced by anticancer drugs is a significant cause of morbidity and mortality. However, most of these reactions are idiosyncratic and are not typically dose-dependent [2, 4]. Diagnosing liver damage due to anticancer agents is particularly challenging because competing etiologies, such as hepatotoxicity due to the intake of other medications, opportunistic infections, radiation therapy, and pre-existing liver disease, are frequent and greatly affect the host's susceptibility to liver injury [2, 4]. The major mechanisms underlying chemotherapy-related hepatotoxicity are based on the production of reactive metabolites, immunological injury, or mitochondrial dysfunction [4]. On the other hand, the spectrum of cancer-associated renal disease has changed in the last decades, mainly due to the introduction of new chemo-radiotherapy regimens. Nevertheless, renal failure remains an important complication of cancer treatment [5, 6]. Considering that drugs are primarily metabolized in the liver and excreted by the kidneys, hepatic and renal impairment can have an unpredictable impact on the metabolism and clearance of drugs that may ultimately affect the treatment outcome and toxicity.

In addition, cardiotoxicity is a common complication not only related to conventional cancer therapy, such as anthracyclines, but also to new antitumoral targeted therapy, such as trastuzumab. Due to the increasing number of patients treated with these agents, the incidence of cardiotoxicity is continuously growing and strongly affecting the patients' quality of life and overall survival, regardless of the oncologic prognosis [3]. Also, peripheral neuropathy is reported by 30-40 % of the patients and is one of the major reasons responsible for cessation of treatment [7]. Certain structural and functional features of peripheral nervous system make it more vulnerable to the action of anticancer drugs, namely the absence of a vascular barrier and of lymph drainage [7]. Furthermore, mammalian nerves are more susceptible to oxidative stress because of their high content of phospholipids, mitochondria rich axoplasm and weak cellular antioxidant defenses. Moreover, the enhanced free radical production promoted by anticancer drugs causes physical damage to neurons [7].

A thorough understanding of the mechanisms of injury is therefore a matter of great importance since it may contribute to detect toxic mechanisms at an early stage of drug development and, importantly, it can contribute to develop strategies aiming to minimize the toxicity. Mitochondrial dysfunction often underlies drug-induced toxicity and the works published over the last years point out that some of the severe adverse effects promoted by anticancer agents involve the targeting of mitochondria [8-11]. The heart, the kidneys, and the central nervous system, which have high energetic demands and are heavily dependent on oxidative phosphorylation, are more prone to the impact of mitochondrial damage. On the other hand, considering the exposure to high concentrations of drugs, the liver is another common organ showing mitochondrial dysfunction [12].

This chapter aims to provide an overview of the mechanisms of mitochondrial dysfunction induced by anticancer drugs and their involvement in several adverse effects, and particularly liver damage. Finally, possible combinations of therapeutic drugs to minimize the mitochondrial dysfunction promoted by these agents are discussed.

http://dx.doi.org/10.5772/59488

2. Methods

We searched literature published in English language included in PubMed for the period of 1970 to 2014. The main keywords searched were "mitochondrial dysfunction", "anticancer drugs and toxicity" and "tissue failure". The remaining papers were found in the reference list of the searched publications.

3. Anticancer drugs-induced tissue injury: The role of mitochondrial dysfunction

Mitochondria are dynamic and multifunctional cytoplasmic organelles, which possess a double membrane: an outer membrane (OMM) that is essentially permeable to ions and solutes up to 14 kDa, and an inner membrane (IMM), which is folded, forming the cristae, which is impermeable to ions and polar molecules. In the IMM are located several transporters, including the ATP/ADP and the aspartate/malate transporters, among others that regulate the movements of molecules across the IMM, and also the multisubunit complexes involved in the oxidative phosphorylation. Between the OMM and the IMM is located the intermembrane space (IMS), whereas the space enclosed by the IMM is the matrix (Fig.1). The IMS contains proteins such as the adenylate kinase and the creatine kinase (CK), as well as the cytochrome *c* and the apoptosis-inducing factor (AIF), which translocate to the cytoplasm during the apoptotic process, and other proteins involved in cellular metabolism. The proteins involved in the Krebs cycle, in the fatty acid oxidation, as well as in the synthesis of the heme and steroids, are located in the matrix [8, 9, 12, 13]. The mitochondrial matrix also contains the mitochondrial DNA (mtDNA). Thus, mitochondria are not only responsible for the synthesis of most of the ATP produced in the cell, but they also play a role in the fatty acid oxidation, the synthesis of the heme, steroids, and polypeptides involved in energy generation, as well as in calcium regulation and cell death. Therefore, taken in account the multitude of essential functions of mitochondria in cells, it is expected that their dysfunction might promote tissue failure, as described below.

3.1. Disturbance of mitochondrial energy production

The NADH and $FADH_2$ generated in metabolic pathways, including glycolysis, fatty acid oxidation and Krebs cycle are oxidized by complexes I and II of the mitochondrial electron transport chain, respectively. The electrons liberated are then passed to ubiquinone (coenzyme Q) that shuttles electrons to complex III, where it is oxidized; the electrons are then passed to complex IV through cytochrome *c*. The electrons carried by cytochrome *c* are used by complex IV to reduce molecular oxygen to water (Fig.1) [8, 14]. According to Peter Mitchell's Chemiosmotic Theory, complexes I, III and IV are redox-driven proton pumps that harness the energy derived from oxidation-reduction reactions to pump protons into the IMS, in parallel to the electron transfer, creating the electrochemical proton gradient (proton motive force) ($\Delta\mu H^+$), which is comprised of two components: a pH gradient (ΔpH)

and a membrane potential (ΔΨ) (Fig. 1). The complex V (ATP synthase), which consists of the F1 subunit, a soluble portion located in the mitochondrial matrix, and the Fo subunit, bound to the IMM, uses the electrical component ΔΨ to phosphorylate ADP to ATP. Thus, the oxidative phosphorylation is coupled to the ATP requirements and the electron flow along the electron transport chain only occurs when the synthesis of ATP is required. The IMM impermeability ensures that the proton pumping along the respiratory chain is coupled to ATP synthesis [8, 12, 14].

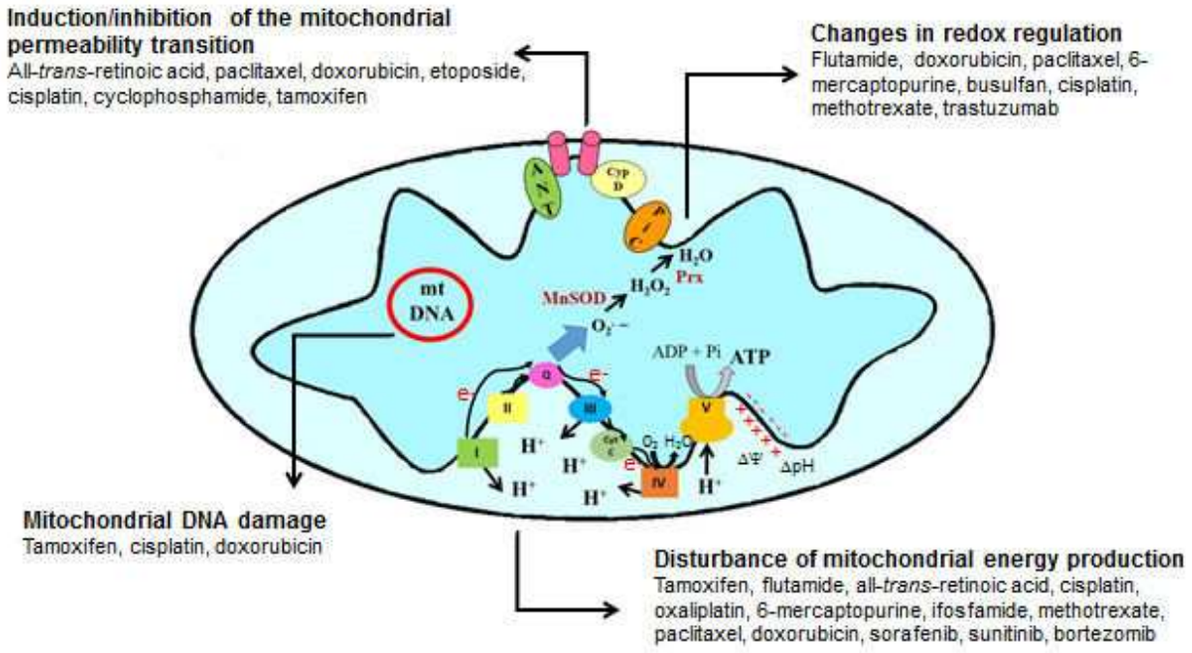

Figure 1. Structure of mitochondria and main mechanisms by which anticancer agents affect mitochondrial functions. Drugs can compromise mitochondrial bioenergetic functions by interfering with the generation system of $\Delta\mu H^+$, by dissipating the transmembrane proton gradient and by directly affecting the complex V or the substrate transporters. Drugs can also trigger or inhibit the mitochondrial permeability transition (MPT) by interfering with the proteins that compose or regulate the MPT or by modulating the critical factors to its onset, which may ultimately lead to cell death. Other drugs induce changes in the redox regulation of mitochondrial functions, promoting several deleterious events, including the interference with oxidative phosphorylation, nutrient oxidation and MPT. Drugs can also damage the mtDNA and, indirectly, compromise the ATP synthesis and favor the production of ROS (ANT, adenine nucleotide translocase; CyPD, cyclophilin-D; Cytc, cytochrome *c*; mnSOD, manganese superoxide dismutase; mtDNA, mitochondrial DNA; PiC, phosphate carrier; Prx, glutathione peroxidase; Q, coenzyme Q).

Xenobiotics can affect mitochondrial bioenergetic functions either by interfering with the generation system of $\Delta\mu H^+$or by causing the dissipation of the transmembrane proton gradient, as well as by affecting directly the F1Fo ATPase and the substrate transporters, including the adenine nucleotide translocase (ANT) and the phosphate–hydrogen co-transporter (phosphate carrier) (Fig.1) [14].

In fact, the inhibition of the electron transport chain by drugs may not only lead to ATP depletion, but also hinders the reoxidation of NADH and $FADH_2$ into $NAD^+$and FAD, respectively, which are required for the activity of several dehydrogenases of the Krebs cycle

http://dx.doi.org/10.5772/59488

and the mitochondrial β-oxidation [15, 16]. In addition, the inhibition of the electron transport chain favors the accumulation of electrons in the electron transport system complexes that can escape and directly react with oxygen to form the superoxide anion radical [17]. The excessive reactive oxygen species (ROS) production can promote several deleterious events (described in more detail in section 3.3), but it is noteworthy that, in this context, both lipid accumulation and lipid peroxidation are favored [15, 16].

On the other hand, drugs can compromise the impermeability of the IMM to protons and dissipate the proton gradient impairing the production of ATP. The IMM impermeability can be surpassed by drugs that either disrupt the mitochondrial membranes or act as ionophores, uncouplers of the oxidative phosphorylation and inducers of the mitochondrial permeability transition (MPT) [12-14]. Moreover, drugs that interfere with the basic components of the phosphorylative system can also impair the production of ATP. These different effects on mitochondria induce changes in cellular bioenergetics, one of the key hallmarks in tissues.

3.2. Mitochondria in Ca^{2+}homeostasis: MPT-dependent cell death

Besides serving as the cells' primary energy source, mitochondria are implicated in the maintenance of calcium homeostasis through calcium uptake and release pathways. The rise of mitochondrial matrix free calcium concentration in the presence of a variety of sensitizing factors can lead to the opening of the MPT pore that may serve either the purpose of providing a fast calcium release or can convey both apoptotic and necrotic death signals.

MPT can be defined as an increase in the IMM permeability to solutes with molecular masses up to 1 500 Da, due to the opening of a voltage and calcium-dependent, cyclosporine A (CyA)-sensitive channel [18].

The molecular identity of the MPT pore is still under debate [19] (Fig. 1). Cyclophilin-D is the binding site for CyA, the golden standard of MPT inhibitors, and among the several components that have been proposed to play a role on MPT, cyclophilin-D is probably the most consensual. The ANT and the voltage-dependent anion channel (VDAC) were also considered key components of the MPT pore complex for many years. Knockout mice devoid of cyclophilin-D are resistant to necrosis promoted by ROS and calcium overload and the mitochondria isolated from the liver, heart and brain of these animals are resistant to MPT *in vitro* [20, 21]. Although these results support a central role for cyclophilin-D, MPT can occur even in the absence of cyclophilin-D if the calcium concentration is high enough [22]. Likewise, MPT can occur in mitochondria lacking ANT, although a higher concentration of calcium is required [23] and, therefore, the ANT is now considered a regulatory component of the MPT pore, rather than a structural one. Similar studies have excluded the VDAC as an essential component of MPT pore megacomplex [24].

The phosphate carrier was also proposed to play a key role in MPT [25], but a later study demonstrated that the reduction of phosphate carrier protein expression does not affect the MPT [26]. A more recent work suggested that the MPT pore complex is composed of ATP synthase dimers and pointed out that cyclophilin-D binds the lateral stalk of the ATP synthase

at the same site as benzodiazepine 423, increasing the sensitivity to calcium [27]. However, the composition of MPT still remains a contentious issue.

Besides the calcium concentration in the matrix, the level of oxidative stress is possibly the most critical factor regulating MPT pore opening. Indeed, both the ANT and cyclophilin D were shown to be modulated by S-oxidation reactions [28-29]. However, other factors may contribute as well: the depletion of adenine nucleotides and high concentrations of phosphate increase the sensitivity of MPT to calcium, while a low pH and a high (negative) $\Delta\Psi$ inhibit MPT pore opening [30].

Drugs can trigger MPT either by interfering with the proteins that compose or regulate the MPT or by modulating the critical factors to its onset (Fig.1) [8]. As a consequence of MPT pore opening, the IMM loses its impermeability to protons, which allows the movement of solutes between the matrix and the cytosol, the dysregulation of cellular ionic homeostasis and the dissipation of $\Delta\mu H^+$. Moreover, since the protein concentration is higher in the matrix, a high osmotic pressure is generated and may lead to mitochondrial swelling, rupture of OMM, and loss of proapoptotic proteins that may trigger the apoptotic pathway in the cytoplasm [30, 31]. These events, together with the bioenergetic failure and the redox catastrophe, can culminate in cell death; if there are no sufficient levels of ATP, necrotic death may predominate over apoptosis [32]. Thus, depending on the cell type involved, different pathological conditions can occur as consequence of MPT induction.

3.3. Changes in redox regulation of mitochondrial functions

During the transfer of electrons along the electron transport chain to oxygen, and particularly at complexes I and III, some of these electrons escape and directly react with oxygen. The univalent reduction of oxygen generates the superoxide anion radical, which is then dismutated by the mitochondrial manganese superoxide dismutase into hydrogen peroxide, a key ROS signaling molecule due to its longer half-life and capacity to diffuse through membranes. The hydrogen peroxide is detoxified into water by the mitochondrial glutathione peroxidase and hence, in normal circumstances, most of the ROS generated by the electron transport chain are neutralized by the mitochondrial antioxidant defenses (Fig.1) [17]. The accumulation of hydrogen peroxide can promote the oxidation of thiolic groups, irreversibly deactivating the protein; likewise, the superoxide anion disassembles Fe–S clusters in several Krebs cycle enzymes and in respiratory complexes, and can combine with nitric oxide to form the highly toxic peroxynitrite. In addition, high levels of ROS can lead to the production of hydroxyl radical, which indiscriminately oxidizes biological macromolecules [33]. Other sources that can contribute to the total mitochondrial ROS include 2-oxoglutarate dehydrogenase, pyruvate dehydrogenase, dihydroorotate dehydrogenase, sn-glycerol-3-phosphate dehydrogenase, electron transfer flavoprotein:ubiquinol oxidoreductase, p66shc/Cytochrome C, Mia40p/Erv1p, and complex II [33]. When maintained within a certain concentration range, ROS act as important signaling molecules, contributing to the redox balance, which regulates the functions that assist the normal cellular physiology [33]. However, the excessive formation of ROS can promote a series of deleterious events that deregulate key mitochondrial functions,

http://dx.doi.org/10.5772/59488

including oxidative phosphorylation, nutrient oxidation and MPT, which may ultimately lead to cell death, tissue failure and have also a key role in disease pathogenesis [33].

3.4. Mitochondrial DNA damage

The mtDNA, maternally inherited, encodes 13 polypeptides that are subunits of the complexes I, III, IV and V, which are synthesized in mitochondrial ribosomes. The majority of the other mitochondrial proteins, including the subunits of complex II, are encoded by nuclear DNA, and imported into mitochondria after synthesis on cytosolic ribosomes [8-10].

The mtDNA is particularly vulnerable to the action of drugs, as it lacks histones, similarly to the bacterial DNA. Furthermore, the DNA repair mechanisms are less efficient that those of nuclear DNA. Therefore, and considering the proximity to the sites where ROS are routinely generated, the frequency of mtDNA mutation is much higher than that of nuclear DNA [13]. Mutations of mtDNA can seriously damage the respiratory chain as most of the polypeptides that form the respiratory chain complexes are encoded by mtDNA. As discussed in section 3.1., the impairment of the respiratory chain decreases the ATP synthesis capacity and enhances the production of ROS, which in turn will promote oxidative damage on several biomolecules, including the mtDNA itself, creating a vicious cycle that further enhances the insult [34].

4. Anticancer drugs impair mitochondria functions: relevance to tissue failure

In the last decades a large number of anticancer drugs have been reported to induce tissue failure by promoting changes in essential functions of mitochondria. The extent and type of mechanisms underlying the anticancer drug-induced mitochondrial dysfunctions are tissue-dependent and responsible for most of the idiosyncratic adverse drug responses.

In this section, we discuss some examples of the prominent members of different groups of anticancer drugs with evidences for the involvement of mitochondrial dysfunction in tissue impairment induced by these compounds.

4.1. Selective estrogen receptor modulators

Tamoxifen has been the endocrine therapy of choice for women with estrogen-receptor positive breast carcinoma over the last decades. Fatty liver is observed in more than 30 % of patients taking tamoxifen, which may persist after the discontinuation of the treatment [35, 36]. Nonalcoholic steatohepatitis, hepatic fibrosis, cirrhosis and hepatic necrosis were also reported [37-39].

Tamoxifen depresses the phosphorylation efficiency and the levels of ATP in a concentration-dependent manner in isolated rat liver mitochondria; these effects were attributed to a decrease in the active ANT content and a partial inhibition of the phosphate carrier [40, 41]. On the other

hand, tamoxifen uncouples liver mitochondria respiration [40, 42] and, at higher concentrations, tamoxifen disrupts membrane integrity [43-44], enhancing the proton leak [40]. Tamoxifen also inhibits the electron transfer along the electron transport chain [40, 42] and the flavin mononucleotide site of complex I was identified as the target of tamoxifen [45]. The interaction of tamoxifen with complex III and IV was also shown [42]. The fact that tamoxifen interferes with membrane dynamics [46] may also decrease the diffusional mobility of membrane proteins and the electron transfer along the electron transport chain [40]. Furthermore, an *in vivo* study pointed out that tamoxifen depletes hepatic mtDNA, which further contributes to inhibit mitochondrial electron transport chain activity, and triggers steatose in mouse liver [47]. Therefore, the effects promoted by tamoxifen on mitochondrial bioenergetics may contribute to the liver damage observed in patients taking tamoxifen (Fig.1).

Interestingly, tamoxifen active metabolites, 4-hydroxytamoxifen and endoxifen, which are responsible for the antitumor actions of tamoxifen [48], do not significantly compromise mitochondrial bioenergetics at the concentrations reached in tissues [49, 50]. These results may indicate that the clinical use of tamoxifen metabolites instead of the prodrug may minimize liver damage. As the outcome of tamoxifen treatment seems to rely on its metabolic activation and endoxifen is a promising drug for cancer treatment, the future utilization of tamoxifen metabolites, and especially endoxifen, deserves further investigation. On the other hand, tamoxifen prevents and reverses the MPT induced by several agents [51-55]. Likewise, tamoxifen metabolites 4-hydroxytamoxifen and endoxifen also prevent and reverse the MPT induced by calcium and phosphate [50, 56]. Although the mechanisms underlying the inhibition of MPT by the antiestrogens are still under debate [57], this protective effect of TAM and its active metabolites regarding MPT might be of interest when considering combined anticancer drug therapies since it can decrease the toxicity of the associated drugs, as discussed in section 5.

4.2. Antiandrogens

Flutamide is a nonsteroidal anti-androgen used in the treatment of advanced prostate cancer, which has been associated with idiosyncratic drug-induced liver injury [58] and, although the mechanisms underlying liver damage are still unknown, mitochondria are a potential target of flutamide.

Indeed, high-doses of flutamide promote hepatocytes death in heterozygous Sod2(+/-) mice, but not in wild-type animals, suggesting that flutamide may exacerbate underlying mitochondrial abnormality [59]. Flutamide leads to the covalent binding of reactive electrophilic metabolites to proteins and diminishes the reduced glutathione (GSH)/glutathione disulfide (GSSG) ratio, as well as the total protein thiols in isolated rat hepatocytes; these effects are associated with the release of lactate dehydrogenase (LDH) [60]. Similar findings were reported by others, which also demonstrated that flutamide increases the hepatic GSSG/GSH ratio, the protein carbonyl levels, and serum lactate levels, supporting the view that the liver damage promoted by flutamide involves oxidative stress and mitochondrondrial dysfunction [59]. Accordingly, the addition of cysteine increased hepatocellular GSH and decreased LDH release in male hepatocytes [60].

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Additionally, flutamide markedly impairs rat liver mitochondrial respiration (mainly at the level of complex I) and decreases the levels of ATP in rat hepatocytes [60]. Moreover, flutamide-treated Sod2(+/-) mice present a decrease in the expression of complexes I and III subunits [59]. Therefore, it seems possible that the increased oxidative stress promoted by flutamide may damage mitochondrial proteins and mtDNA, particularly when the antioxidant system is compromised [59], contributing to liver damage (Fig.1).

4.3. Alkylating agents

4.3.1. Platinum analogs

Cisplatin, which crosslinks DNA, is widely used in the treatment of head, neck, bladder ovarian and testicular cancers, but it has also been used in the management of other malignancies. Unfortunately, cisplatin promotes severe side effects, and particularly nephrotoxicity [61] and neurotoxicity [62].

Peripheral neuropathy is the dose limiting side effect of cisplatin and occurs in 30 % of patients. Dorsal root ganglion neurons treated with cisplatin exhibit mitochondrial vacuolization and degradation both *in vitro* and *in vivo*, suggesting that mitochondrial damage is involved in cisplatin-induced neurotoxicity (Fig.1) [63]. Besides covalently binding to nuclear DNA [64], cisplatin also directly binds to mtDNA, hindering the transcription of mitochondrial genes [63]. Another platinum analog, oxaliplatin, affects both complex I- and complex II-mediated respiration and decreases ATP production in rat peripheral nerve axons [65]. Acetyl-l-carnitine, which inhibits the development of oxaliplatin-evoked neuropathy, prevents oxaliplatin-induced mitochondrial dysfunction, further implicating mitochondria in the etiology of peripheral neuropathy [65].

About a quarter to one third of patients undergoing cisplatin treatment experience nephrotoxicity, which is manifested clinically as lower glomerular filtration rate and reduced serum magnesium and potassium levels [61]. Although the mechanism underlying cisplatin nephrotoxicity is not yet clear, the available evidence suggests that mitochondrial dysfunction plays a key role in renal tubular cell injury and death. Ultrastructural analysis of cisplatin-treated renal tubular cells of mouse kidney demonstrates the decrease in mitochondrial mass, disruption of cristae, and extensive mitochondrial swelling [66], supporting the involvement of mitochondria in cisplatin-induced nephrotoxicity. Cisplatin decreases manganese superoxide dismutase and complex II activity in rodents' kidney [67]. The GSH-reductase activity and the levels of GSH are markedly diminished in porcine proximal tubular cells [68]. These observations suggest that cisplatin strongly reduces the antioxidant defenses and favors ROS formation. However, agents that are able to prevent ROS formation, do not prevent cell death, suggesting that ROS formation is not the direct cause of cell death [68]. Furthermore, cisplatin significantly impairs kidney mitochondrial bioenergetic functions. In porcine proximal tubular cells, cisplatin inhibits complexes I to IV and decreases intracellular ATP [68]. In fact, the kidney of animals treated with cisplatin presents decreased mtDNA content and reduced complex I, III and IV protein expression [67].

Cisplatin is a rare cause of hepatotoxicity (steatosis and cholestasis) at standard doses, but high doses may lead to liver damage, revealed by abnormal liver tests, especially aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [69]. Light microscopic observations confirmed that high doses of cisplatin cause massive hepatotoxicity; alterations at the ultrastructural level, including atrophied mitochondria, were also found [70]. Cisplatin induces MPT in rat liver mitochondria [71]. Moreover, cisplatin stimulates state 4 respiration, but does not affect FCCP-uncoupled respiration, suggesting that cisplatin affects mitochondrial bioenergetics by increasing the IMM permeability to protons and not by interfering with respiratory chain complexes activity [71]. Both the induction of MPT and the effects on liver mitochondrial bioenergetics are prevented by thiol group protecting agents, suggesting that changes on the redox-status of thiol groups affect membrane permeability to cations and underlie liver mitochondrial dysfunction [71]. Accordingly, it was proposed that the mechanism of cisplatin-induced hepatotoxicity involves membrane rigidification, lipid peroxidation, oxidative damage of cardiolipin and protein sulfhydryl groups, as well as decreased GSH/GSSG ratio, ATP, GSH and NADPH [72].

4.3.2. Nitrogen mustards

Cyclophosphamide is an alkylating agent used in the treatment of lymphomas, multiple myeloma, and certain types of leukemia, retinoblastoma, neuroblastoma, ovarian cancer, and breast cancer. Generally, cyclophosphamide does not cause relevant cardiotoxicity, but when it occurs, it appears to be related to a single dose, unlike the anthracyclines [3]. Patients who were previously medicated with anthracyclines or that underwent chest irradiation are more prone to suffer from cyclophosphamide-induced cardiotoxicity [3]. Liver damage was also reported [73, 74].

Cyclophosphamide compromises calcium accumulation by heart or liver mitochondria, which can almost be restored by CyA [75]. As the increases in the levels of serum AST, serum ALT, glucose-6-phosphate dehydrogenase and creatine phosphokinase induced by cyclophosphamide can also be attenuated by the simultaneous administration of CyA, the induction of MPT is closely related to the hepatotoxicity and cardiotoxicity promoted by cyclophosphamide (Fig.1) [75].

Ifosfamide, another nitrogen mustard, is one of the most commonly implicated drugs in kidney injury [76]. Using mitochondria isolated from the kidney of rats treated with ifosfamide, it was shown that this alkylating agent significantly inhibits complex I, resulting in NADH elevation and NAD^+depletion, and Krebs cycle impairment (Fig.1) [77]. Among the ifosfamide metabolites, only chloroacetaldehyde, which reaches high concentrations in the renal cortex, inhibits complex I, suggesting that this metabolite is responsible for the ifosfamide-induced nephrotoxicity [77].

4.3.3. Alkyl sulfonates

Busulfan is an alkylating drug, which forms DNA intrastrand crosslinks, used in the clinical management of chronic myelogenous leukemia. Although in standard doses busulfan rarely

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causes liver dysfunction, some cases of hepatotoxicity during busulfan treatment were reported [78-80].

The toxicity of busulfan is thought to involve oxidative stress mechanisms as it promotes decreases in GSH in hepatocytes both *in vivo* and *in vitro* [81]. Considering that glutathione S-transferase inhibitors and antioxidants prevent busulfan toxicity *in vitro*, it is likely that busulfan toxicity requires glutathione conjugation [81] Moreover, the effects of busulfan are strongly exacerbated on GSH-depleted hepatoctyes [81], which may provide a basis to explain the enhanced sensitivity to the liver damaging effects of busulfan under certain circumstances.

4.4. Enzyme inhibitors

4.4.1. Anthracyclines

Doxorubicin is used in the clinical management of a wide range of cancers, and particularly in breast cancer treatment. The anticancer activity of doxorubicin involves its intercalation into DNA and disruption of topoisomerase-II-mediated DNA repair, as well as the generation of ROS that lead to lipid peroxidation, as well as membrane and DNA damage [82]. However, its therapeutic use is limited by its side-effects, mainly the dose-dependent myelosuppression and the cumulative and irreversible cardiotoxicity, which in the most severe forms may lead to patient death [83].

Acute cardiotoxicity occurs in less than 1 % of the patients immediately after infusion and is usually reversible; the early-onset chronic progressive form affects 1.6–2.1 % of patients, during therapy or within the first year after treatment; the late-onset chronic progressive form occurs after one year of completion of therapy in 1.6–5 % of patients, supporting the need of long-term follow-up [3]. Doxorubicin causes myocardial damage as shown by the increase in serum levels of AST, ALT, LDH isoenzyme and creatine phosphokinase isoenzyme [84]. Doxorubicin-induced cardiotoxicity etiology seems complex, and several effects may be involved, triggering a domino effect [83]. Among the several mechanisms postulated, the induction of oxidative stress is the most widely accepted. The univalent reduction of the tetracyclic ring of anthracycline by complex I generates a semiquinone free radical; the unpaired electron of this semiquinone is transferred to oxygen, forming the superoxide radical, while the tetracyclic ring returns to the parent quinone [85]. The free radicals generated are thought to be related to the interference with calcium homeostasis and bioenergetic functions, lipid peroxidation, and mtDNA damage, which play a key role in the pathogenesis of doxorubicin cardiotoxicity (Fig.1).

Heart mitochondria isolated from rats treated with doxorubicin present decreased state 3 respiration and respiratory control ratio (RCR), whereas the state 4 respiration is not affected [86-88]; complex I activity is also inhibited [87]. Besides affecting nuclear DNA, doxorubicin damages mtDNA [89-91] and decreases its content in human hearts [90]. Accordingly, doxorubicin-exposed human hearts show low activity of complex I and IV (encoded by mtDNA) but not of complex II (exclusively encoded by nuclear DNA) [90]. The higher levels of superoxide in doxorubicin-exposed hearts correlate negatively with mtDNA content and with the activities of respiratory chain complexes encoded by mtDNA [90]. The damage

leading to mtDNA adducts, as well as the higher rate of ROS formation and depression of GSH in heart tissue, persist for several weeks after cessation of doxorubicin treatment [92, 93].

Furthermore, mitochondria isolated from the heart of rats treated with doxorubicin present diminished ability to accumulate calcium [84, 86, 87, 94]. Similar effects were reported in mitochondria isolated from doxorubicin-treated human atrial trabeculae, and were shown to be reversed by CyA [95]. Considering that the decrease in left ventricular fractional survival promoted by doxorubicin is improved by the simultaneous administration of CyA, it seems that doxorubicin-induced heart damage is closely related to the induction of MPT pore opening [84, 96]. As discussed in section 3.3, oxidative stress is a major factor regulating MPT and doxorubicin leads to the oxidation of mitochondrial glutathione and to the accumulation of membrane disulfides, which may contribute to MPT induction. On the other hand, it has been proposed that the ANT is a key target for doxorubicin, as following doxorubicin treatment the amount of ANT protein and its active content are reduced in rats [94, 97]. The effects of doxorubicin on the ANT explain both the MPT induction and the effects on mitochondrial respiration [97]. Indeed, the decrease in state 3 respiration observed in heart mitochondria isolated from doxorubicin-treated rats is partially reversed by CyA or dithiothreitol, but not by trolox, suggesting that the toxic effects of doxorubicin on mitochondrial bioenergetics are at least in part a consequence of MPT induction and involve changes in the redox state of thiol groups [88]. Noteworthy, among several agents, including antioxidants, CyA was the only agent that was able to reverse the doxorubicin-induced alterations in the calcium accumulation capacity when added *ex vivo* [94]. Although the triggering of MPT by doxorubicin may initially involve the oxidation of regulatory components of the MPT pore megacomplex, once it occurs thiol protecting agents are unable to restore the pore to its original closed state [94, 98]. Therefore, antioxidants may be useful in the preventive setting, as discussed in section 5. Moreover, by increasing the generation of free radicals, doxorubicin also significantly enhances lipid peroxidation, as well as alterations in proteins and biomolecules that act as signaling molecules [99-101].

Altogether, the results obtained so far suggest that the persistent nature of doxorubicin cardiotoxicity reflects a self-perpetuating mechanism, where mtDNA alterations accumulate, leading to a damaged respiratory chain and decreased calcium loading ability; the defective respiratory chain further enhances ROS generation and mtDNA insult (Fig.1) [83, 98].

The heart is the main target of doxorubicin toxicity, due to the abundance of mitochondria in heart tissue, the elevated rate of oxygen consumption and the lower antioxidant defenses [83]. However, mitochondrial dysfunction has also been observed in other tissues. Indeed, in isolated mitochondrial fractions from the brain of rats treated with doxorubicin, the thiobarbituric acid-reactive substances and the vitamin E levels are increased, whereas the reduced glutathione content is diminished [102]. In addition, doxorubicin increases the sensibility of brain mitochondria to MTP pore opening [102]. The use of doxorubicin was also associated with a higher risk for developing hepatotoxicity among breast cancer patients [103]. Liver mitochondria isolated from doxorubicin-treated rats present decreased RCR and the activity of complex IV is inhibited [107]. In addition, light microscopic observations confirmed that

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doxorubicin at high doses caused massive liver injury; alterations at the ultrastructural level, such as atrophied mitochondria, were shown [70].

4.4.2. Topoisomerase inhibitors

Etoposide is a podophyllotoxin derivative used in the treatment of several cancers that acts as a topoisomerase II inhibitor. Cases of hepatic injury were reported using either standard doses [104] or high-dose regimens [105]. Etoposide induces calcium-dependent MPT in rat liver mitochondria [106]. Since the etoposide-induced MPT is prevented by several antioxidants, it was proposed that etoposide triggers MPT pore opening through the generation of oxidant species, which is further corroborated by the ability of antioxidants to prevent the apoptosis promoted by etoposide (Fig.1) [107]. Therefore, the generation of oxidant species that are able to induce mitochondrial dysfunction may contribute to hepatic injury.

4.5. Antimicrotubules — Taxanes

Paclitaxel is a taxane-derived drug used in monotherapy or in combination with other agents, for the treatment of ovarian, breast and advanced non-small cell lung cancers, and AIDS-related Kaposi's sarcoma.

Painful peripheral neuropathy is the major dose-limiting side-effect of paclitaxel therapy, with the major drawback that the pain and sensory abnormalities can persist for months or years. Moreover, it may turn the patients unable to complete optimal chemotherapy schedules thus potentially compromising the treatment efficacy [108].

The involvement of mitochondrial dysfunction in paclitaxel-induced pain is suggested by the presence of swollen and vacuolated neuronal mitochondria [109]. Earlier investigations demonstrated that paclitaxel promotes a CyA-sensitive swelling in liver, kidney, heart, and brain mitochondria; the highest degree and slope of the swelling are observed in liver mitochondria, whereas the lowest are detected in brain mitochondria [110].

Using a rat model of paclitaxel-induced pain, it was shown that the non-specific ROS scavenger N-tert-butyl-α-phenylnitrone significantly decreases paclitaxel-induced mechanical hypersensitivity, whereas the superoxide selective scavenger 4-hydroxy-2, 2, 6, 6-tetramethylpiperidine-1-oxyl (TEMPOL) does not present significant effects [108]. Therefore, the authors suggest that ROS are involved in the development and maintenance of paclitaxel-induced pain, although such effects cannot be attributed to superoxide radicals alone [108]. Moreover, rat sciatic nerve samples taken after induction of painful peripheral neuropathy with paclitaxel exhibit significant impairment of both complex I- and complex II-mediated respiration and deficits in ATP synthesis; the mitochondrial dysfunction promoted by paclitaxel is abrogated by acetyl-l-carnitine, again supporting that paclitaxel promotes oxidative damage [65].

Paclitaxel is extensively excreted by the liver, and therefore its administration to patients with liver impairment should be handled with care [69]. Alterations of liver functions are seen in 4-17 % of patients treated with doses up to 190 mg/m^2, but they can occur in 16-37 % of patients taking higher doses [69].

In isolated liver mitochondria, paclitaxel induces large amplitude swelling, the dissipation of mitochondrial membrane potential and the release of cytochrome c; these effects are inhibited by CyA, suggesting that paclitaxel induces MPT pore opening [110]. Paclitaxel also significantly increases complex IV-mediated ROS production (Fig.1) [110]. Paclitaxel does not inhibit mitochondrial respiration, but ROS formation is abolished by complex IV inhibitors, suggesting that paclitaxel promotes ROS production not by inhibiting the respiratory complexes, but through an effect on complex IV [110]. The abrogation of ROS formation does not prevent paclitaxel-induced MPT, suggesting that the induction of MPT is not secondary to enhanced ROS generation [110]. The combination with doxorubicin enhances the induction of oxidative stress [111].

The cardiotoxicity promoted by paclitaxel is usually represented by subclinical sinus bradycardia (approximately 30 % of patients), but more severe conditions were also reported [3]. A recent study suggests that microtubule disorganization in cardiac myocytes promoted by paclitaxel leads to MTP pore opening [112]. However, when isolated mitochondria are exposed to paclitaxel, no significant effects are detected; the authors suggested that paclitaxel does not promote MPT due to a direct effect on mitochondria [112]. However, it must be noted that lower concentrations were used in the latter study in comparison with previous work using liver mitochondria [110, 112].

Therefore, both the induction of MPT and mitochondrial ROS production can contribute to paclitaxel side effects in the nerve, liver, kidney and heart.

4.6. Antimetabolites

4.6.1. Folate antagonists

Methotrexate is a folic acid antagonist widely used in the treatment of leukemia and other malignancies. Gastrointestinal toxicity and liver function abnormalities are common in patients taking methotrexate and the use of methotrexate in patients with history of liver disease is not advisable [113].

In liver mitochondria, methotrexate promotes a significant rise in superoxide radical formation, as well as in lipid peroxidation, whereas the GSH levels are decreased [114]. Likewise, methotrexate significantly impairs the function of isolated heart mitochondria by promoting lipid peroxidation, mitochondrial swelling and by inhibiting complex I, II and IV activities [115].

Methotrexate administration also leads to small intestinal injury and damages in enterocyte mitochondria, as shown by the decrease in the RCR, an indicator of mitochondrial function [116]. Moreover, the activities of complexes II and IV are markedly decreased in enterocyte mitochondria, suggesting that the deleterious effects promoted by methotrexate on enterocyte mitochondria can compromise ATP synthesis (Fig.1) [116], thereby leading to the gastrointestinal toxicity seen in patients.

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4.6.2. Purine analogs

6-Mercaptopurine is an orally administered immunosuppressive drug used to treat acute lymphocytic leukemia. 6-Mercaptopurine is converted to its active metabolites, the 6-thioguinine nucleotides, or inactivated by xanthine oxidase or by thiopurine methyltransferase to 6-thiouric acid or 6-methylmercaptopurine, respectively [117]. Liver injury is an important adverse effect of 6-mercaptopurine, with an estimated frequency of liver test abnormalities within 1-9 % range [118]. Clinically relevant concentrations of 6-mercaptopurine are toxic to rat hepatocyte cultures by a mechanism that involves oxidative stress and ATP depletion (Fig. 1) [119]. The decreased rat hepatocytes viability promoted by 6-mercaptopurine is nearly prevented by allopurinol (xanthine oxidase inhibitor) together with trolox (vitamin E analog), implying xanthine oxidase-mediated metabolism of the thiopurines and oxidative stress in the hepatotoxicity promoted by 6-mercaptopurine [119].

4.7. Retinoids

All-*trans*-retinoic acid was approved in 1995 by the Food and Drug Administration for the treatment of acute promyelocytic leukemia, changing the outcome of this disease, which was associated with a significant mortality until then. Retinoids induce hepatotoxicity, either during dietary supplementation [120] or treatment of acute promyelocytic leukemia patients [121], and hypertriglyceridemia [122]. Moreover, vitamin A supplementation in rats induces slight enlargement of mitochondria [123], hepatic oxidative insult and mitochondrial dysfunction [124], supporting the view that mitochondria are a target of retinoid toxicity.

All-*trans*-retinoic acid is a known inducer of MPT pore opening [125-127], which is thought to reflect its ability to modulate ANT activity in both liver and heart mitochondria [126]. All-*trans*-retinoic acid depresses the phosphorylation efficiency of mitochondria and, at higher concentrations, induces uncoupling of mitochondria [127]. Whereas earlier studies attribute the uncoupling promoted by retinoids to an increase in the IMM permeability [128], a more recent study suggests that the leak of protons through the Fo fraction of complex V is the underlying mechanism [127]. Thus, is seems likely that the liver injury promoted by all-*trans*-retinoic acid reflects its effects on mitochondria (Fig.1).

4.8. Targeted therapy

4.8.1. Monoclonal antibodies

Trastuzumab is a recombinant humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), which is overexpressed by many adenocarcinomas. Trastuzumab improves cancer patient survival, but it also causes cardiotoxicity in a significant number of patients, ranging from 2-7 % when used as monotherapy, 2-13 % when used combined with paclitaxel, and up to 27 % when trastuzumab is used with both anthracyclines and cyclophosphamide [3]. In contrast to the cardiomyopathy promoted by doxorubicin, the cardiac dysfunction induced by trastuzumab does not appear to be dose dependent and is often reversible [123]. Neonatal rat cardiomyocytes treated with an inhibitory HER2 antibody

exhibit an increased ROS production and cell death, which are reversed by N-acetylcysteine and by CyA, suggesting that the toxic effects of trastuzumab on the heart involve mitochondrial damage and enhanced ROS production (Fig.1) [129].

4.8.2. Tyrosine kinase inhibitors

Sorafenib is effective against renal-cell carcinoma and hepatocellular carcinoma, whereas sunitinib is used in the management of advanced kidney cancer, gastrointestinal stromal tumor, and pancreatic neuroendocrine tumors. In phase I–II trials, 11 % of patients taking sunitinib experienced cardiovascular events and approximately half of the patients developed hypertension [130]. The incidence of sorafenib-associated heart toxicity is lower than that of sunitinib, and hypertension occurred in about 17 % of patients in clinical trials [131].

Sorafenib compromises mitochondrial function at clinically relevant concentrations in a myoblastic cell line grown under conditions where cells are either glycolytically or aerobically poised; the other tyrosine kinase inhibitors investigated (imatinib, dasatinib, sunitinib) do not affect the mitochondria [132]. Sorafenib uncouples heart mitochondria and inhibits complex V and complex II+III; at much higher concentrations the complex I and IV are also inhibited (Fig.1) [132].

Using neonatal rat cardiomyocyte cultures, it was shown that sunitinib decreases the mitochondrial membrane potential, and that both sunitinib and sorafenib reduce the intracellular ATP levels [133]. Echocardiographic abnormalities are apparent in sorafenib, but not in sunitinib or pazopanib treated animals; the analysis of ventricular cardiomyocytes revealed that sunitinib promotes mitochondrial swelling, dense deposits, and matrix cavitation, whereas sorafenib disrupted mitochondrial cristae [133].

4.8.3. Proteasome inhibitors

Bortezomib is a proteasome-inhibitor approved for the treatment of multiple myeloma and mantle cell lymphoma and its use in other types of cancer is currently under investigation. However, bortezomib induces dose-limiting peripheral neuropathy and compromises complex I- and complex II-mediated respiration, as well as ATP production in peripheral nerve axons, suggesting that mitochondrial dysfunction plays a key role in bortezomib-induced peripheral neuropathy (Fig.1) [134].

Mechanism	Drug class	Target organ	References
MPT			
MPT induction			
All-*trans*-retinoic acid	Miscellaneous agents	Heart and liver	[125-127]
Paclitaxel	Antimicrotubules	Heart, liver, kidney	[110]
Doxorubicin	Enzyme inhibitors	Heart and brain	[84, 86, 87, 94, 95, 102]
Etoposide	Enzyme inhibitors	Liver	[106]
Cisplatin	Alkylating agents	Liver	[71]

Mechanism	Drug class	Target organ	References
Cyclophosphamide	Alkylating agents	Heart and liver	[75]
MPT inhibition			
Tamoxifen	SERMs	Liver	[51-55]
Mitochondrial bioenergetics			
Tamoxifen	SERMs	Liver	[40, 41, 159]
Flutamide	Antiandrogens	Liver	[59, 60]
All-*trans*-retinoic acid	Miscellaneous agents	Liver	[127]
Cisplatin	Alkylating agents	Liver and kidney	[67, 68, 71]
Oxaliplatin	Alkylating agents	Nerve	[65]
6-Mercaptopurine	Antimetabolite	Liver	[119]
Ifosfamide	Alkylating agents	Kidney	[77]
Methotrexate	Antimetabolites	Heart and GI	[115, 116]
Paclitaxel	Antimicrotubules	Nerve	[65]
Doxorubicin	Enzyme inhibitors	Heart and liver	[86-88]
Sorafenib	Targeted Therapy	Heart	[132, 133]
Sunitinib	Targeted Therapy	Heart	[133]
Bortezomib	Targeted therapy	Nerve	[134]
mtDNA damage			
Tamoxifen	SERMs	Liver	[47]
Cisplatin	Alkylating agents	Neurons and kidney	[63, 67]
Doxorubicin	Enzyme inhibitors	Heart	[89-91]
Oxidative stress			
Flutamide	Antiandrogens	Liver	[59, 60]
Doxorubicin	Enzyme inhibitors	Heart and brain	[85, 102]
Paclitaxel	Antimicrotubules	Liver and nerve	[108, 110]
6-Mercaptopurine	Antimetabolites	Liver	[119]
Busulfan	Alkylating agents	Liver	[81]
Cisplatin	Alkylating agents	Kidney and liver	[67, 68, 72]
Methotrexate	Antimetabolites	Heart and liver	[114, 115]
Trastuzumab	Targeted therapy	Heart	[129]

Table 1. Summary of the mechanisms of mitochondrial dysfunction promoted by anticancer agents (GI, gastrointestinal tract; MPT, mitochondrial permeability transition; mtDNA, mitochondrial DNA; SERMs, selective estrogen receptors modulators).

5. A mitochondrial basis for anticancer drugs combinations: a promising approach to therapy

The severe toxicity promoted by anticancer agents represents a substantial health care burden that may seriously affect the treatment outcome. Based on the previous sections, mitochondria take center stage within the toxicity mechanisms, and are in the first line for protection by

pharmacological strategies aiming to avoid alterations that may prove deleterious both in the short and in the long term. Considering that some of these effects are irreversible or cumulative, it is desirable to prevent these events when planning the therapy of cancer patients.

As discussed in the previous section, oxidative stress has been established as one of the primary cause of mitochondrial dysfunction and toxicity induced by anticancer agents and, therefore, several antioxidants have been tested *in vitro* and *in vivo* as a prophylactic measure. In particular, naturally occurring antioxidants have been investigated as therapeutic adjuvants, as they are considered safe and well-tolerated, and may afford protection against cancer treatment-related toxicity by improving mitochondrial functions.

Alpha-lipoic acid affords protection against the neurotoxic effects promoted by cisplatin and paclitaxel through its antioxidant and mitochondrial regulatory functions [135]. The toxic effects promoted by cisplatin on rat liver mitochondria are also prevented by thiol group protecting agents [71]. Curcumin, which has anti-inflammatory and anticancerous properties, counteracts the mitochondrial lipid peroxidation and GSH levels alterations in mitochondria isolated from the brain and liver of rats treated with cisplatin, suggesting that it can abrogate the toxic effects of cisplatin on brain and liver [136]. Likewise, epicatechin prevents the renal damage and mitochondrial dysfunction promoted by cisplatin by decreasing oxidative stress; noteworthy, epicatechin does not compromise the antitumor actions of cisplatin in HeLa cells [67].

The etoposide-induced MPT is prevented by ascorbate, the primary reductant of the phenoxyl radicals generated by etoposide, and by thiol protecting agents [107].

An *in vitro* study demonstrated that Vitamin E decreases the oxidative stress induced by methotrexate in rat heart mitochondria and thereby minimizes mitochondrial dysfunction [115]. Likewise, the administration of lipoic acid decreases oxidative stress induced by methotrexate, which affects liver mitochondrial function [114].

Acetyl-L-carnitine completely blocks the effects of bortezomib on mitochondria and pain [134].

Strategies to prevent doxorubicin-induced cardiotoxicity are probably the best studied, given the significant number of patients affected and the impact on the overall success of the treatment. Many studies reported that antioxidants could afford cardioprotection against doxorubicin therapy. The broad antioxidant resveratrol markedly ameliorates the cardiac dysfunction promoted by doxorubicin, while the ROS generation is decreased, and glutathione, superoxide dismutase and catalase activities are improved [137]. Also, flavonoids, and particularly 7-monohydroxyethylrutoside, protect against the cardiac toxic effects promoted by doxorubicin both *in vitro* and *in vivo* [138]. In addition, 7-monohydroxyethylrutoside does not compromise the antitumor activity of doxorubicin in human ovarian cell lines and in the corresponding mouse xenograft models, and even inhibits the overexpression of adhesion molecules promoted by doxorubicin on vascular endothelial cells [138]. The combination of doxorubicin and vitamin E-succinate cooperates to induce apoptosis in human gastric cancer cells, by promoting doxorubicin influx and suppressing its efflux [139]. On the other hand, vitamin E also aggravates the heart damage promoted by doxorubicin in P388 tumor-bearing mice [140].

http://dx.doi.org/10.5772/59488

Studies in animals demonstrated that the inhibition of mitochondrial respiration and the decrease in mitochondrial calcium accumulation capacity promoted by doxorubicin are prevented by the coadministration of the beta-adrenergic receptor antagonist carvedilol [87]. The prophylactic use of carvedilol in patients receiving doxorubicin contributes to maintain left ventricle diameters constant and to preserve diastolic function [141]. Interestingly, the toxic effects promoted by doxorubicin on heart mitochondria and cardiac cell apoptosis are prevented by carvedilol, but not by atenolol, another beta-adrenergic receptor antagonist with no antioxidant action, suggesting that the antioxidant properties and not the beta-adrenergic receptor antagonism are responsible for the cardioprotective effects of carvedilol [142]. Likewise, metoprolol, which also has no antioxidative properties, failes to afford cardioprotection in lymphoma patients treated with doxorubicin [143].

Dexrazoxane, a well-studied therapeutic adjuvant for doxorubicin chemotherapy, is a free radical scavenger that was found to have cardioprotective effects by preventing the functional damage of cardiac mitochondria initiated by ROS [83, 144]. Dexrazoxane prevents or reduces cardiac injury in doxorubicin-treated children with acute lymphoblastic leukemia without affecting the antitumor activity of doxorubicin [145]. In contrast, other iron chelators have failed to afford the same degree of cardioprotection, suggesting that iron does not play a crucial role in the oxidative stress-mediated toxicity of doxorubicin [138, 146, 147].

Promising results were obtained when the potent phosphodiesterase-5 inhibitor sildenafil is combined with doxorubicin. Prophylactic treatment with sildenafil prevents cardiomyocyte apoptosis and left ventricular dysfunction in a mouse chronic model of doxorubicin-induced cardiotoxicity [148]. On the other hand, in breast cancer cells, sildenafil enhances sensitivity to doxorubicin without enhancing its toxicity in bone marrow cells or macrophages [149]. Furthermore, cotreatment with sildenafil enhances doxorubicin-induced apoptosis in prostate cancer cells and inhibits tumor growth in mice bearing prostate tumor xenografts, while attenuating left ventricular dysfunction promoted by doxorubicin [150].

Interesting results were also observed when retinoids and antiestrogens are combined. Antiestrogenic compounds inhibit the MPT-induced by retinoids in isolated liver mitochondria [127, 151, 152]. Noteworthy, the prevention of MPT by antiestrogens does not compromise the antitumor efficacy of all-*trans*-retinoic acid, as an additive/synergistic action was demonstrated in breast cancer [153-156] and melanoma [157] cell lines. Therefore, we propose that studies *in vivo* with combined therapies are now required to confirm that these results obtained *in vitro* will translate into more therapeutic benefits in humans while attenuate mitochondrial dysfunctions promoted by drugs used individually.

6. Concluding remarks

Considering the key role played by mitochondria in cell survival and death, the pharmacological modulation of mitochondrial activity has been investigated in cancer therapy [13, 158]. It is thought that this strategy may overcome the resistance mechanisms related with conventional chemotherapy that do not target mitochondria directly, but interfere with signaling

pathways which lie upstream of mitochondria and that are frequently deregulated in cancer [158]. However, the targeting of mitochondria as a therapeutic strategy is often compromised by the absence of significant pathophysiological differences between mitochondria in normal and malignant cells, leading to reduced selectivity of drugs targeting mitochondria. Therefore, the actions that are beneficial in cancer cells may, in contrast, underlie some of the severe toxic effects promoted by these agents.

Indeed, the induction of mitochondrial damage is an important contributor for some of the most well-known toxic effects of anticancer agents, namely the liver injury promoted by tamoxifen [159], the cardiotoxicity of doxorubicin or the cisplatin-induced neuropathy and nephrotoxicity. Organ dysfunction has a significant impact on the treatment outcomes and, therefore, the better understanding of the mechanisms of toxicity may unveil strategies to limit, or preferably to prevent, the incidence of these events and thereby improve the overall clinical success.

The recognition that mitochondrial dysfunction plays a key role in drug-induced toxicity may contribute to identify the drugs that are more likely to lead to such effects at an early stage. In this context, the use of isolated mitochondria fractions is a valuable tool to predict drug safety, since it provides relevant information while allowing to reduce the number of laboratory animals and the costs of preclinical studies [8].

On the other hand, our current knowledge does not allow to predict the idiosyncratic injury related with drug-induced mitochondrial dysfunction. It seems that genetic, metabolic and environmental factors that impair mitochondrial function can add their effects to those of anticancer drugs, compromising mitochondrial function to an extent where manifestations start to occur [17]. Therefore, therapeutic drug monitoring is mandatory. Furthermore, as organ damage may become apparent months or even years after the completion of the treatment (e.g. late-onset doxorubicin toxicity) the need of long-term follow-up is reinforced.

Finally, future studies should aim to develop strategies which are able to afford protection against both the short-term and long-term effects of anticancer drugs and without compromising their antitumor activity. Although antioxidants showed promise in *in vitro* studies, inconsistent results and failure in clinical trials turn the use of antioxidants as adjuvants in cancer therapy hardly consensual [7, 83]. However, in this context, we need to take into consideration that antioxidants may present different intracellular localization patterns and interfere with normal redox signaling pathways in specific cell compartments; an approach involving the targeted delivery of antioxidants to mitochondria can possibly provide better outcomes [7, 83]. Moreover, there are important differences between *in vitro* and *in vivo* toxicities and between animal models and humans. The different drug metabolism and clearance, as well as the asymmetries in redox regulation may account for the difficulty in translating these strategies into human subjects [83].

In conclusion, studies in suitable animal models are vital for a better understanding of the mechanisms underlying drug toxicity and the benefits of strategies aiming to prevent mitochondrial damage. So far most studies have used animal models devoid of tumors, which add an extra physiological burden that may influence the effects of drugs [83]. Moreover, as

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described in the previous section, some of the toxic effects on mitochondria are observed in several organs, including the liver and kidneys, which may compromise both the pharmacokinetics and the efficacy of the anticancer drugs, but also the benefit of therapeutic adjuvants aiming to protect the mitochondria. These observations emphasize the importance of performing *in vivo* studies in relevant models, as well as the crucial importance of the clinical control and therapeutic drug monitoring of patients treated with anticancer drugs.

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