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Drugs targeting mitochondrial functions to control tumor cell growth

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Abstract

Mitochondria, the power houses of the cell, are at the cross-road of many cellular pathways. They play a central role in energy metabolism, regulate calcium flux and are implicated in apoptosis. Mitochondrial dysfunctions have been associated with various physiopathological disorders, especially neurodegenerative diseases and cancer. Structurally diverse pharmacological agents have shown direct effects on mitochondria ultra-structures and functions, either at the DNA level or upon targeting proteins located in the inner or outer mitochondrial membranes. The brief review deals with the molecular targets and mechanisms of action of chemically diverse small molecules acting on specific mitochondrial loci, such as the respiratory chain, DNA biogenesis, potassium channels, the Bcl-2 protein and the permeability transition pores (PTP). Drugs, which specifically compromise the structural and functional integrity of mitochondria, may provide novel opportunities to combat cancer cell proliferation, providing that these molecules can be selectively delivered to tumor sites. Different examples reported here show that mitochondrial insult or failure can rapidly lead to inhibition of cell survival and proliferation. Mitochondrial impairment may be a successful anti-cancer strategy.

Keywords: Mitochondria; Cancer chemotherapy; Apoptosis; Respiratory chain; Permeability transition pore

For the past four decades, mitochondria have raised a large interest due to their key implication in many pathways essential to both the life and death of cells. These organelles generate by oxidative phosphorylation 80–90% of ATP needed for cell respiration and survival, regulate calcium flux and play an important role in the integration of pro- and anti-apoptotic stimuli. Together with chloroplasts, mitochondria are unique as subcellular organelles containing their own genome. Mitochondrial DNA (mtDNA) mutations have been associated with multiple disorders, ranging from neurodegenerative diseases to cancer. Cancer cells exhibit mitochondrial dysfunction, genetic instability with alterations, such as mutations, deletions or translocations and are highly glycolytic [1].

The central role of mitochondria in mediating programmed cell death has led to an interest in exploiting radio- and chemo-therapeutic agents to trigger cancer cell death [2]. The vast majority of conventional anti-cancer drugs indirectly exploit mitochondria to exert their cytotoxic action, via multiple activation pathways implicating p53 or death receptors, for examples. However, targeting directly mitochondrial function could be of significant therapeutic relevance since the rapid and continuous growth of tumor cells is highly energy-dependent and since cancer cells often develop drug resistance, leading to a resistance to pro-apoptotic signals. As a consequence, mitochondria now appear as reservoirs of potential targets for anti-cancer therapy and various approaches to interfere with the vital mitochondrial functions in cancer cells have been proposed [3]. An updated survey of the different classes of mitochondria-targeted anti-cancer agents is presented here together with an account of emerging mitochondria-based anti-cancer strategies. Different approaches (Fig. 1) to target mitochondria with small molecules are presented here. We concentrated our efforts on anti-cancer agents but there are many other mitochondria-targeted therapeutic agents used or developed for the treatment of other diseases, in particular neurodegenerative and cardiovascular diseases, as well as diabetes and certain viral infections [3]. The primary

Abbreviations: ANT, adenine nucelotide transporter; KCO, potassium channel openers; MCR, mitochondrial respiratory chain; MMP, mitochondrial membrane permeability; PBR, peripheral benzodiazepine receptor; PTP, permeability transition pore; ROS, reactive oxygen species; SOD, superoxide dismutase; VDAC, voltage-dependent ion channel

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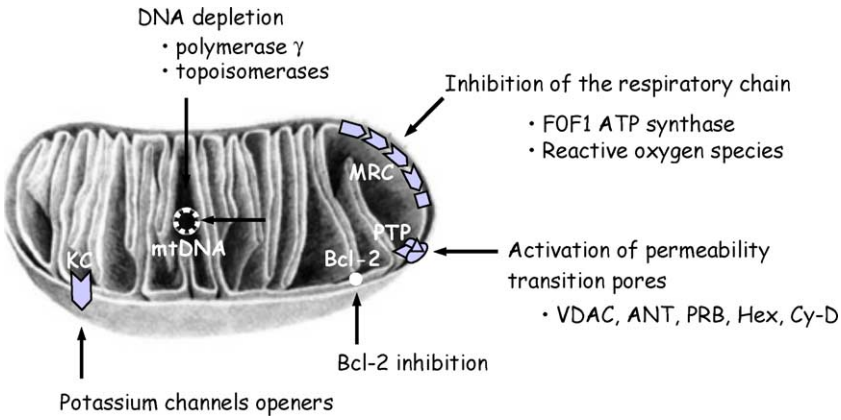

Fig. 1. Schematic illustration of sites of action of mitochondria-targeted drugs discussed here.

objective of this review is to establish a repertoire of the different categories of mitochondria-interacting drugs and to mention some of the structural and functional differences between normal and tumor mitochondria, which could be exploited to develop anti-cancer agents. Thus far, we must admit that the idea of targeting directly and specifically mitochondria to obtain a persistent anti-tumor response has not been plainly successful but, as reported here, there are encouraging signs of activity in several cases. Efforts must continue to identify tumor-associated targets within mitochondria and to design small molecules active selectively against these mitochondrial targets.

1. Mitochondria and mtDNA biogenesis

While the precise contribution of mitochondria to carcinogenesis remains unclear, it has been reported that mtDNA mutations, ranging from a single base mutation to a large deletion, were detected in a variety of tumors [4]. The analysis of the complete mitochondrial genome of 10 colorectal cancer cell-lines has shown that seven displayed mtDNA point-mutations that were not detected in normal tissue from which the tumor is derived (somatic mutation) [5]. To date, no particular mtDNA mutations have been correlated to a specific cancer. Mutations might affect the rate of mtDNA replication and cells that lack mtDNA gene expression may become more sensitive to apoptosis induction [6]. However, in several cancer cell-lines, mtDNA mutations contribute to the chemotherapy resistance [7]. Selective mtDNA targeting or depletion might thus be a profitable option to inhibit tumor cell proliferation or survival.

The characteristics of mtDNA, which is not protected by histones and presents a limited repair capacity, make it an attractive target for pharmacological agents. A wide range of structurally different drug (Fig. 2) has shown selective properties in decreasing mtDNA levels that were correlated to cytotoxicity. For example, anti-viral nucleoside analogs, such as 3′-azido-3′-deoxythymidine (AZT, zidovudine) or 2′-3′-dideoxycytidine (ddC, zalcitabine), used to treat human immunodeficiency virus (HIV) and hepatitis B infections, cause impaired mtDNA metabolism leading to a reduction of cellular mtDNA level and cytotoxicity [8]. Some of those nucleoside analogs reduce mtDNA synthesis through the inhibition of the mitochondrial DNA polymerase γ that mediates mtDNA replication, or through an earlier termination of DNA strand elongation due to their deficiency in 3′-hydroxyl groups [9]. Even though these nucleoside analogs have shown in vitro properties in depleting mtDNA in mammalians cells leading to delayed loss in cell growth and viability, the exact role of mitochondria in the mechanism of action of those drugs remains to be clarified. In addition to impairing mtDNA polymerase γ function, 3′-azido-3′-deoxythymidine is also known to inhibit telomerase, ADP/ATP mitochondrial translocator activities and oxidative phosphorylation enzymes [10,11]. Because AZT is not specific to mitochondria, the role of these organelles in the drug action is difficult to establish precisely.

Several reports have demonstrated that certain DNA intercalating agents, such as ethidium bromide or the dimeric anti-cancer drug ditercalinium, can also cause mtDNA depletion in cultured mammalian cells [12,13]. These cells, called ρ^0, are respiratory deficient but can be maintained by glycolysis alone. The mechanism by which these intercalating agents inhibit mtDNA synthesis and not nuclear DNA is not fully understood but it might involve a preferential accumulation in mitochondria [14] rather than the nucleus and might act, as shown recently for ditercalinium, through the disruption of mtDNA replication via an interaction with the mitochondrial polymerase γ and the mitochondria-specific Twinckle helicase [13].

mtDNA metabolism can also be targeted by topoisomerase inhibitors. Both types I and II topoisomerases have been identified in mitochondria and different known topoisomerase inhibitors were shown to inhibit the mitochondrial enzymes. Bacterial 4-quinolone analogs, such as nalidixic acid and ciprofloxacin, have been shown to cause mtDNA depletion, mitochondrial respiration loss, glycolysis increase and delayed growth [15]. The epipodophyllotoxin VM-26 (teniposide) inhibits topoisomerase II extracted from mitochondria and induces mtDNA breaks

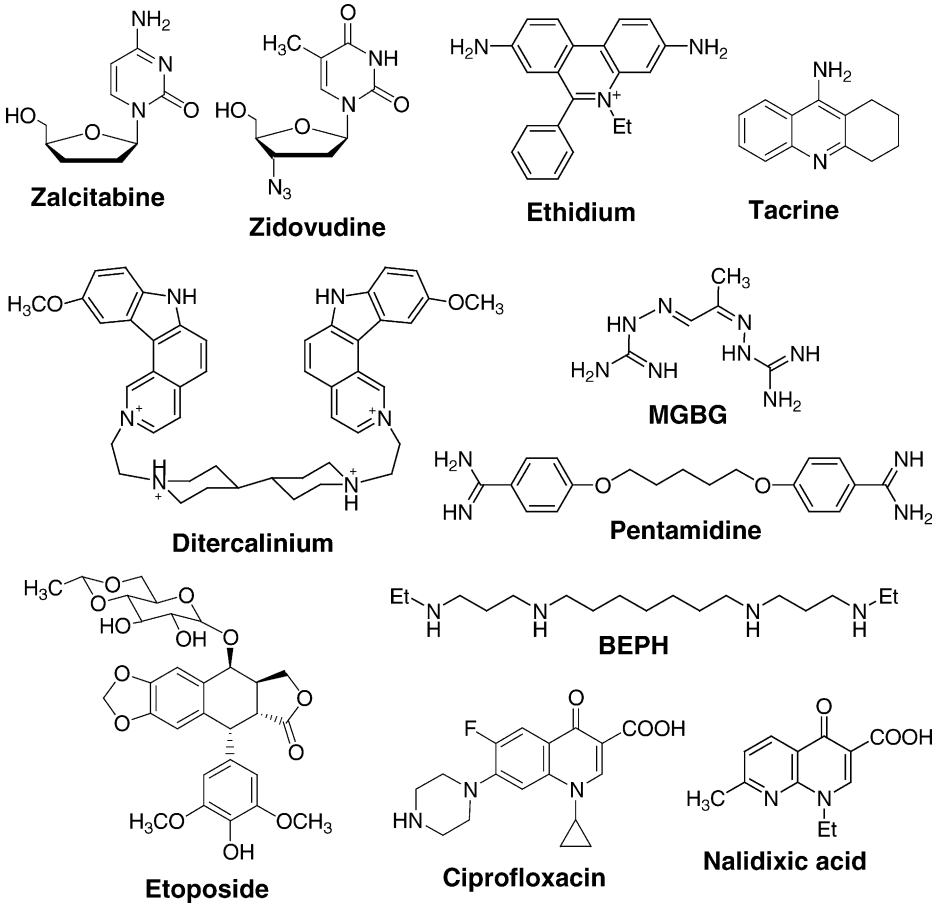

Fig. 2. Drugs inducing mitochondrial DNA depletion.

[16]. Similarly, the prototypic topoisomerase II-targeted anti-cancer drug etoposide has revealed mitochondrial inhibitory properties. Treatment with a low concentration of etoposide (10 μM) results in nuclear DNA damages that affect mitochondria through caspase-2 activation and cytochrome *c* release [17]. In contrast, at a higher concentration (50 μM), cytochrome *c* release is caspase-independent and seems to be related to permeability transition pore (PTP) formation [17].

2. Mitochondria and inhibition of the respiratory chain

It has long been accepted that cancer cells depend on glycolysis to fulfill their energetic needs (ATP synthesis) indicating that mitochondria and particularly the mitochondrial respiratory chain (MRC) might be inefficient. Therefore, drugs targeting the respiratory chain might be more toxic to tumor cells than to normal cells.

Alterations in the ''respiratory function'' have been associated with an increase in the mitochondrial energy metabolism of reactive oxygen species (ROS) production. However, the exact factors contributing to ROS generation remain unclear. Mitochondrial DNA codes for 13 respiratory chain subunits – 7 for the NADH-ubiquinone oxidoreductase (complex I), 1 for the ubiquinone–cytochrome *c* oxidoreductase (complex III), 3 for the cytochrome oxidase (complex IV) and 2 for the ATP synthetase (complex V)—mutations in the mtDNA might directly affect the function of the respiratory chain. mtDNA mutations correlate with increased ROS generation in primary leukemia cells isolated from patients with chronic lymphocytic leukemia [18]. These biochemical changes brought on the concept that cancer cell are under ''persistent oxidative stress'' [19] leading to genetic instability, cellular proliferation and anti-cancer drug resistance that might contribute to disease progression. This concept has also helped the development of novel therapeutic drugs that inhibit the respiratory chain or that activate apoptotic or necrotic pathways through increased generation of ROS.

Early studies of the electron transport chain had brought a number of efficient and specific drugs. The flow electrons from NADH to oxygen through complex I, ubiquinone, complex III, cytochrome *c*, complex IV (and through complex II from the oxidation of succinate) was defined with the help of major inhibitors, such as rotenone to inhibit complex I, malonate to inhibit complex II, myxothiazole and antimycin A to inhibit complex III, cyanide to inhibit complex IV and oligomycin or protonophores,

such as the carbonyl cyanide *p*-chlorophenylhydrazone (ClCCP) to inhibit the ATP-synthase [20]. It is interesting to note here that 2-methoxy-antimycin lacks inhibitory effects on electron transport but binds directly to Bcl-X_L/Bcl-2 proteins to trigger apoptosis [21]. Rotenone, which was initially used to understand the electron transport to oxygen in the mitochondrial respiratory chain, inhibits complex I in a non-competitive manner and increases ROS generation inducing apoptosis in primary leukemia cells [20].

Over the years, potent synthetic and naturally-occurring inhibitors endowed with desirable pharmacological properties (e.g., more stable and more specific uptake in particular tissues) have been identified (Fig. 3). This is the case for a range of polyphenolic phytochemicals acting on the F_0F_1-ATP synthase [22]. The natural stilbene phytoalexin piceatannol was found to be a more potent inhibitor of the F_0F_1-ATP synthetase (IC_{50} ~8–9 μM) than the chemopreventive agent resveratrol (3,4′,5-trihydroxy-trans-stilbene) or isoflavones, such as the flavonoid genistein (IC_{50} ~15–20 μM), or natural estrogens, such as 17α-estradiol and 17β-estradiol (IC_{50} >50 μM). Both piceatannol and resveratrol inhibit the F_1 complex of the enzyme, whereas the two estrogens preferentially target the F_0 complex. The inhibition of F_0F_1-ATPase by resveratrol and genistein is non-competitive. Certain *N*-methylpyridinium and quinolinium cations potently inhibit the mitochondrial electron transfer of complex I. This is the case in particular for compounds MQ18 (*N*-methyl-2-*n*-dodecyl-3-methylquinolinium) and MP6 (*N*-methyl-4-[2-methyl-3-(*p*-*tert*-butylphenyl)]propylpyridinium) which both selectively inhibit the electron transfer process, with

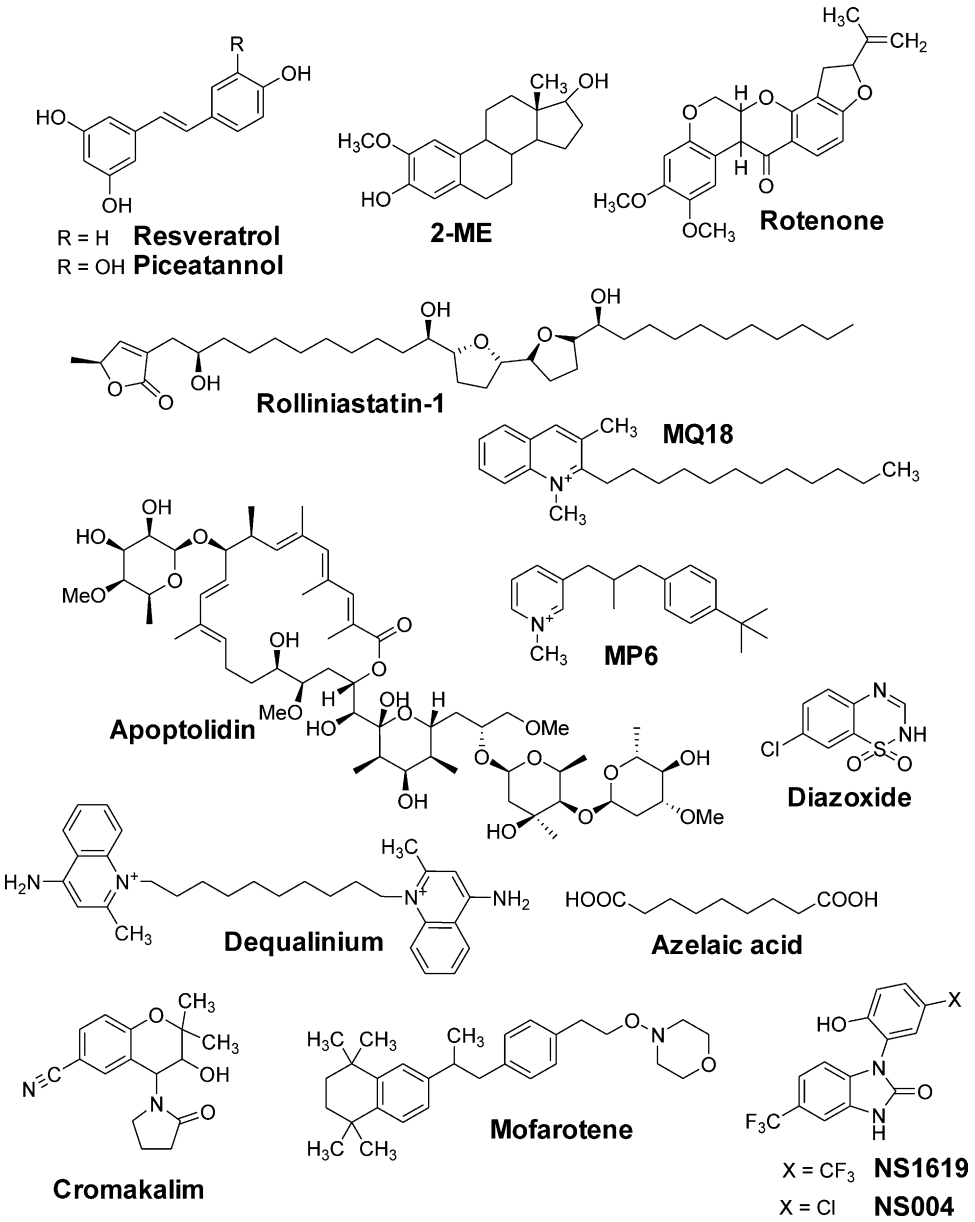

Fig. 3. Drugs targeting the respiratory chain, producing ROS or acting as potassium channels openers.

micromolar affinities, via a selective interaction with one of the two ubiquinone binding sites of the enzyme [23].

The mitochondrial F_0F_1-ATP synthase is the privileged target of a family of cytotoxic macrolides which includes cytovaricin and ossamycin. The polyketide natural product apoptolidin (Fig. 3), which also belongs to this group of mitochondria-targeted products, is one of the most cell-line selective cytotoxic agents tested against the 60 cell-lines panel of the NCI and a potent pro-apoptotic product [24]. This work and others make F_0F_1-ATP synthase a promising target for the identification of anti-tumor agents. Inhibition of the mitochondrial respiratory chain can be exploited to develop anti-cancer agents. Bis-tetrahydrofuranic derivatives of Annonaceous acetogenins, including rolliniastatin-1 (originally isolated from *Rollinia membaranacea* seeds), are among the most potent inhibitors of the MRC complex I and are effective tumor cell proliferation inhibitors. They are developed as anti-cancer agents [25].

During the mitochondrial metabolic process, the generation of reactive oxygen species, in particular superoxide anion, hydrogen peroxide and hydroxyl radical, can occur at complexes I or III. Under physiological conditions, an appropriate level is needed for the stability of the redox balance and cellular proliferation. An accumulation of such reactive oxygen species can be toxic for the cells. ROS are usually eliminated by metabolic enzymes, such as superoxide dismutase (SOD), catalase and various peroxidases. Targeting those enzymes or increasing the intracellular production of ROS by xenobiotics, ultraviolet or ionizing irradiations, causes various damages that can lead to cell death. Although the cell-damaging effects of oxygen free radicals can be associated with pathological disorders, the use of appropriate agents that induce ROS production, such as rotenone [26], might also provide an interesting approach to preferentially kill cancer cells. For example, 2-methoxyestradiol (2-ME), which is used in photodynamic anti-cancer therapy, causes an accumulation of ROS by inhibition of the SOD activity and ensuing cytotoxic effects [27]. The combination of agents that simultaneously increase ROS production and inhibit ROS elimination might be useful to limit cancer cell growth. For example, the combination of 2-ME with rotenone enhances cellular $O_2^{\bullet -}$ radical accumulation and triggers apoptosis [28].

3. Mitochondrial potassium channel interference

Increasing the permeability of the mitochondrial membrane to protons or potassium by opening mitochondrial potassium channels induces a decrease of the mitochondrial membrane potential ($\Delta\psi$) (depolarization), swelling of the mitochondria, decrease in ATP synthesis and cytochrome *c* release [29]. Various drugs, such as diazoxide, the vasorelaxant cromakalim (Fig. 3) and its analogs EMD-60480 and EMD-57970 were identified as mitochondrial potassium channel openers (KCO) [30]. The cromakalims are essentially studied as vasodilatating and anti-hypertensive agents but cromakalim itself was shown to inhibit the growth of SK-N-MC human neuroblastoma and U-373 MG human astrocytoma cell-lines in a dose-dependent manner [31]. In contrast, certain KCO rather activate tumour cell growth. This is the case for the KCO minoxidil which was shown to stimulate growth of MCF-7 human breast cancer cells whereas the K^+ channel-blockers dequalinium (Fig. 3) and amiodarone had marked inhibitory effects on the same cell proliferation [32]. This is perhaps because the mitochondrial K^+ channels share the same pharmacological properties as the plasma membrane K^+ channels. Therefore, there is a need to find specific mitochondrial channel interacting drugs. The benzothiadiazine diazoxide (Fig. 3) was shown to affect mitochondrial K^+ transport 1000 times more potently than the plasma membrane one [33]. This compound protects from rotenone-induced death of cultured neuronal PC12 cells [34]. It depolarizes respiration-dependent mitochondrial membrane potential, reduces the rate of proliferation and arrests human acute leukemic T cells in the G0/G1 phase [35]. In the same category of K^+-ATP channel openers, it is worth mentioning the drug levosimendan currently developed for the treatment of acute and decompensated heart failure. The capacity of levosimendan to activate K^+ flux to the mitochondrial matrix is believed to account for its anti-ischemic action [36]. KCO can exert quite distinct pharmacological effects depending on the recipient cell type.

A massive depolarization of mitochondria coupled with an inhibition of the MRC has been observed in glioma cells with large-conductance potassium channel openers NS1619 (1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)-phenyl]-5-(trifluoromethyl)-2H-benzimidazol-2-one) and NS004 (5-trifluoromethyl-1-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benzimidazole-2-one) (Fig. 3). But this direct mitochondrial effect was without effect on the survival of the glioma cells [37]. Similarly, concentrations of rotenone that block electron flow through mitochondrial complex I do not alter either the growth or viability of human lymphoma cells [38]. In other cases, it seems that there is a link between MRC inhibition and the anti-proliferative activity. Indeed, this is the case for azelaic acid (Fig. 3), a naturally occurring straight-chained 9-carbon atom dicarboxylic acid used for the treatment of lentigo maligna melanoma [39] and for the arotinoid mofarotene (Ro40-8757) (Fig 3) which couples inhibition of oxidative phosphorylation with inhibition of Burkitt lymphoma cell proliferation and apoptosis [40].

4. Mitochondria and anti-cancer drug-induced apoptosis

There is no doubt that mitochondria play a central role in programmed cell death. Some mitochondrial deregulations have been described as the hallmarks of apoptosis: loss of

mitochondrial membrane potential ($\Delta\psi$), disruption of electron transport and oxidative phosphorylation, generation of active oxygen species and release of pro-apoptotic factors, such as cytochrome *c*, Smac/Diablo, AIF, etc., that trigger activation of caspases. Because mitochondria play a pivotal role in triggering apoptosis, there is a major interest in exploiting their pro-apoptotic function to reduce tumor cell growth and survival. Two essential apoptosis-related pharmacological approaches have been considered: inhibition of the Bcl-2 proteins family and the permeability transition pores. They are discussed here in turn.

4.1. Bcl-2 targeting

The inhibition of mitochondrial membrane permeability (MMP), which avoids cytochrome *c* release, contributes to the anti-apoptotic functions of the Bcl-2 protein localized in the mitochondrial external membrane [41]. Different strategies have been developed to overcome the anti-apoptotic effect of the Bcl-2 family proteins. Abrogate expression of Bcl-2 or its close cousin Bcl-X_L was shown by a single-chain antibody [42] or by antisense single-stranded oligonucleotides which can hybridize to the target mRNA and inhibits its translation into the Bcl-2 protein. In this vein, the combination of Genasense (Oblimersen sodium, gp3139), an 18-mer phosphorothioate antisense oligonucleotide targeted to the bcl-2 mRNA, with conventional cytotoxic drugs has revealed encouraging results [43] even if the monotherapy with the antisense is strongly compromised [44]. An alternative strategy is to develop small molecules, which mimic the dimerization domain BH3 identified in essentially all Bcl-2 related proteins. The interaction of such small molecules with Bcl-2 induces caspase-dependent apoptosis of tumor cells. This is the case for the cell-permeable chromene

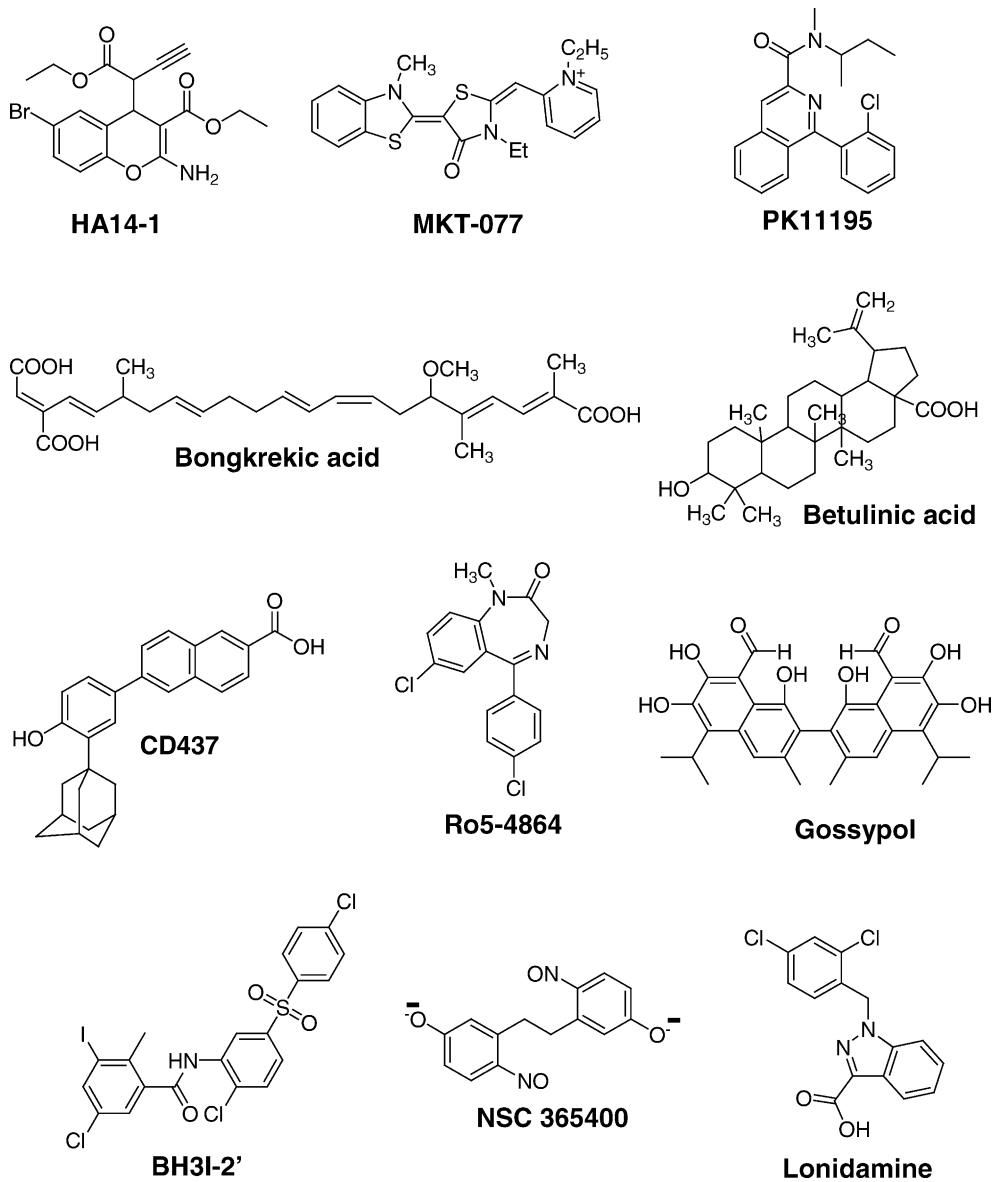

Fig. 4. Drugs targeting Bcl-2 or the permeability transition pores.

derivative HA14-1 (ethyl 2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)4H-chromene-3-carboxylate) (Fig. 4) which binds to the Bcl-2 surface pocket and induces apoptosis [45]. Other non-peptidic small molecules antagonists of Bcl-2 and Bcl-X_L are currently developed [46], such as the diazocine dioxide derivative NSC365400 (Fig. 4) and the thiazolidine compound BH3I-2 (Fig. 4). This later molecule is an inhibitor of BH3 peptide binding to Bcl-X_L [21]. The most recent example in this category of Bcl-2 targeted drug is the naturally occurring polyphenolic compound gossypol (Fig. 4), which possesses in vivo anti-cancer properties in addition to being a contraceptive agent. Very recently, the (−) enantiomer of gossypol was shown to overcome apoptosis resistance by specifically targeting proteins of the Bcl-2 family [47].

4.2. Permeability transition pore activation

Alterations of the mitochondrial membrane permeability have been found to play a major role in the apoptotic pathway. A sudden break-down of the membrane potential ($\Delta\psi$), detected by the fluorescence dissipation of cationic lipophilic fluorochromes, such as 3,3′-dihexyloxacarbocyanine iodide (DiOC6(3)), rhodamine 123, or 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethylbenzimidazolcarbocyanine iodide (JC-1) is often associated with the formation of a megapore, the permeability transition pore in the inner membrane. In the cyanine dyes family, there is also the anti-cancer drug MKT-077 (Fig. 4) that was initially considered as a mitochondria-specific molecule. The compound presents tolerable toxicities in animals and the intravenous administration of MKT-077 inhibits tumor growth in xenograft models and prolongs mice survival [48]. However, phase I clinical trials have revealed that this product exhibits renal toxicity and the clinical development was discontinued [49]. It is worth mentioning also here that this delocalized lipophilic cation was also found to bind to the perinuclear hsp70 family protein mortalin-2 (mot-2) [50]; it should therefore not be considered as a mitochondria-specific molecule sensu stricto.

The composition and structure of the PTP result from the association of several proteins, namely the adenine nucleotide translocase (ANT) localized in the mitochondrial inner membrane, the voltage-dependent ion channel (VDAC) in the outer membrane and the mitochondrial peripheral benzodiazepine receptor (PBR) and the peptidyl-prolyl isomerase cyclophilin D (Cyp-D). This protein complex creates a channel that links the mitochondrial matrix to the cytosol [51]. The aperture of this channel allows the free passage of small molecules of up to 1.5 kDa, and the dissipation of the proton gradient that impairs the respiratory chain function. The entrance of solutes and water leads to the matrix swelling and the outer membrane rupture, allowing the release of caspase-activating proteins, such as cytochrome *c*.

A number of experimental chemotherapeutic agents directly affect MMP by inhibiting PTP opening through direct binding to one of the PTP protein components (Figs. 4 and 5). For example, cyclosporin A, a potent immunosuppressant drug, binds with a high affinity to cyclophilin D thereby inhibiting the opening of PTP. This inhibition is independent of the cyclosporin A immunosuppressive properties because the *N*-methyl-Val-4-cyclosporin analog is still able to block PTP but fails to inhibit calcineurin and to block cytokine genes [52]. The binding of cyclosporin A to PTP prevents necrotic cell death from oxidative stress, Ca^{2+} ionophore toxicity and ischemic injuries [53]. PTP opening can also be inhibited not by direct drug binding but by preventing Ca^{2+} accumulation by agents, such as thapsigargin, an endoplasmic reticulum Ca^{2+}-APTase inhibitor [54]. This inhibition usually triggers apoptosis in various cell-lines.

Thapsigargin and cyclosporin A both inhibit the opening of PTP. The reverse situation has been reported recently with dinuclear gold(I)–carbene complexes [55] and with a plant product named sophoranone (Fig. 5), an isoprenoid-substituted flavonoid extracted from the traditional Chi-

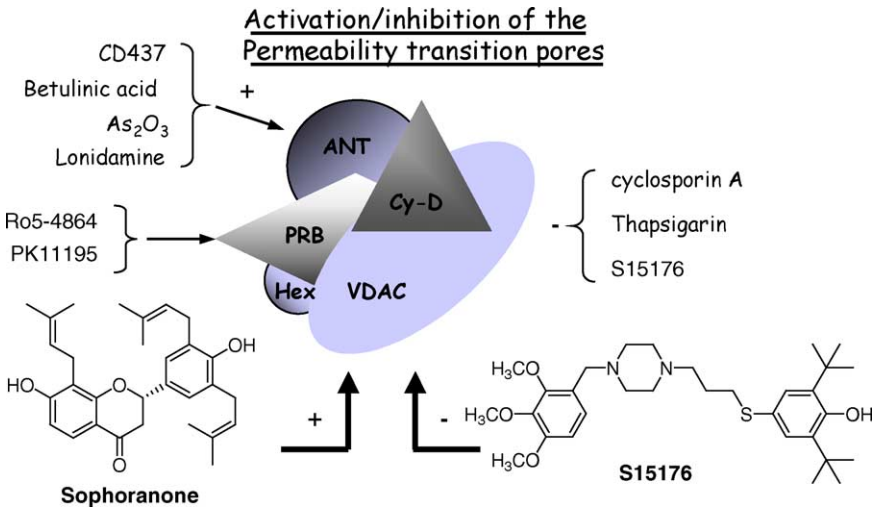

Fig. 5. Schematic of the permeability transition pore (PTP) and drugs interfering with various protein components of the PTP.

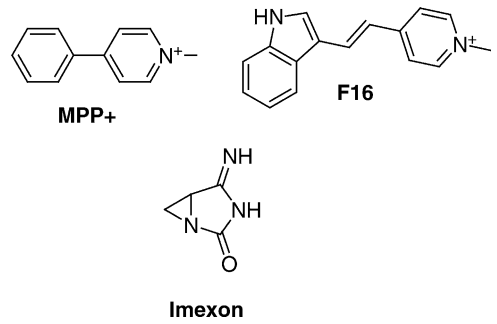

Fig. 6. Other mitochondria-targeted drugs.

nese medicine *Shan Dou Gen* which is isolated from the roots of *Sophora subprostrata*. Sophoranone induces the production of ROS outside mitochondria and induces the opening of PTP, thus releasing cytochrome *c* to induce apoptosis of U937 leukemia cells [56]. The main target of sophoranone has not yet been precisely characterized but this mitochondria targeted plant product warrants further investigations as a potential anti-cancer agent.

A particularly interesting small molecule targeting mitochondria is the *N*-methylpyridinium compound F16 (Fig. 6), which selectively inhibits proliferation of mammary epithelial cells over-expressing the erb-2/neu proto-oncogene or other oncogenes, such as c-*myc* and v-Ha-*ras* [57]. This structurally simple lipophilic compound, identified through a high-throughput chemical library screen, accumulates in mitochondria to cause selective dysfunctions in these organelles via a dissipation of the proton gradient established across the inner mitochondrial membrane (decrease of $\Delta\psi$). The mitochondrial damaging activity of F16 would be at the origin of its ability to trigger apoptosis or necrosis depending on the genetic background of the target carcinoma cell [58]. This discovery strongly reinforces the interest in finding mitochondriotoxic small molecules. A cautionary note should however be introduced at this stage because the structure of F16 resembles that of 1-methyl-4-phenylpyridinium (MPP^+ in Fig. 6), a well-known parkinsonism-causing toxin (metabolically produced after oxidation of the nigrostriatal neurotoxin MPTP) which inhibits the replication of mitochondrial DNA [59].

The lupane-type triterpene betulinic acid (3β-hydroxy-lup-20(19)lupaen-28-carbonic acid) [60], lonidamine [61], arsenic trioxide (one of the most successful treatments for acute promyelocytic leukemia) and 6[3-adamantyl-4-hydroxyphenyl]-2-naphtalene carboxylic acid (CD437 in Fig. 4) [62] induce MMP via a direct effect on ANT. However, even though these agents have a similar effect on MMP, they seem to trigger apoptosis via divergent pathways [63]. The inhibition of oxidative phosphorylation by the F_0F_1-ATPase inhibitor oligomycin sensitizes the cells to lonidamine-induced cell death, whereas both inhibition of oxidative phosphorylation and glycolysis are needed to sensitize the same cells to arsenic trioxide-induced death [63]. However, there is a controversy regarding the nature of the exact target of the arsenic trioxide. Using a VDAC polyclonal antibody (which specifically inhibits VDAC-mediated cytochrome *c* release induced by Bax and Bak) and liposomes containing purified VDAC protein, VDAC was characterized as a primary biological target for As_2O_3 [64]. In fact, the mechanism of action of As_2O_3 is pleiotropic and implicates dissipation of $\Delta\psi$ coupled with a release of cytochrome *c* [64] as well as the inhibition of the mitochondrial respiratory function through the increase of ROS generation to promote apoptosis in primary leukemia cells [65]. This compound is also known to provoke the degradation of the PML-RARα fusion protein in acute promyelocytic leukemia cells [66]. The situation is apparently clearer with lonidamine (Fig. 4), which triggers apoptosis via a direct effect on the mitochondrial permeability transition pore [61]. Several clinical trials for the treatment of advanced solid tumors with lonidamine-containing regimens have shown promising results [67].

The peripheral benzodiazepine receptor, located in the mitochondrial outer membrane, participates to the PTP regulation. A series of PBR-specific ligands were characterized with the benzodiazepine Ro5-4864 and isoquinoline carboxamide PK11195 (Fig. 4) being the two most widely used PBR-binding compounds [68,69]. These two molecules have opposite pharmacological effects. PK11195 tends to block PBR whereas Ro5-4864 strongly protects human lymphoblastoid cells from tumor necrosis factor-α induced apoptosis. The anti-apoptotic effect of Ro5-4864 can be blocked by PK11195 [69]. This later isoquinoline derivative potentiates apoptosis induced by different chemotherapeutic drugs and is believed to inhibit drug efflux mediated by the P-glycoprotein [70]. This type of compound might thus be useful in combination chemotherapy regimens. The exploitation of the PBR as a target for anti-cancer agents has been recently discussed in details [71].

The last mitochondria-selective drug to mention is the aziridine-containing iminopyrrolidone drug imexon (Fig. 6), which exhibits selective growth-inhibitory potency for multiple myeloma. This cyanoaziridine derivative induces oxidative stress, mitochondrial dysfunctions and apoptosis in myeloma cells through the covalent reaction with biologically important sulfhydryl compounds [72]. RPMI8226/I myeloma cells resistant to imexon present important morphological alterations of their mitochondria and enhanced expression of anti-apoptotic mitochondrial proteins, such as Bcl-2 [73]. The potent pro-apoptotic activities of imexon coupled with its selective interaction with mitochondria make this molecule an interesting lead compound for the development of tumor-active aziridino-iminopyrrolidones.

5. Conclusion

Small molecules can make profit of various key components of mitochondria. The ‘‘doors’’ and channels that

protect and cross the mitochondrial membranes can be selectively blocked by drugs and in other cases the nucleic acids accumulated inside the organelles can be selectively eliminated. All these approaches provide chemical opportunities to affect the mitochondrial functions, as summarized in Table 1. The pharmacological control of mitochondria is feasible. Whether or not these routes and targets are suitable to block the proliferation of tumor cells remain to be seen but encouraging results have been reported recently with the discovery of mitochondriotoxic molecules, such as compound F16 endowed with marked tumor cell growth inhibitory properties [57]. There is no doubt that apoptosis can be massively activated with the use of compounds targeting key protein components of the mitochondria (e.g., F_0F_1-ATP synthase, Bcl-2, ANT). Certain conventional, clinically used anti-cancer drugs (e.g., etoposide as well as paclitaxel and vinorelbine [74]) exert a direct action mitochondria in addition to their primary cytosolic or nuclear effects. Other anti-tumor agents, such as CD437 and ditercalinium, appear to be more specific to

Table 1
Summary of mitochondria-targeting drugs and their potential targets

Drug	Potential target	Reference
3′-Azido-3′-deoxythymidine (AZT)	mtDNA biogenesis, ATP mitochondrial translocator	[8,9,11]
Ethidium bromide	mtDNA biogenesis	[12]
Ditercalinium	mtDNA biogenesis	[13]
Nalidixic acid	mtDNA biogenesis	[15]
Ciprofloxacin	mtDNA biogenesis	[15]
Teniposide	mtDNA biogenesis	[16]
Etoposide	mtDNA biogenesis	[17]
Rotenone	Respiratory chain/complex I	[20]
MQ18	Respiratory chain/complex I	[23]
MP6	Respiratory chain/complex I	[23]
Rolliniastatin-1	Respiratory chain/complex I	[25]
Ro40-8757	Respiratory chain/complex I	[40]
Malonate	Respiratory chain/complex II	[20]
Myxothiazol	Respiratory chain/complex III	[20]
Antimycin A	Respiratory chain/complex III	[20]
ClCCP	Respiratory chain/complex IV	[20]
Resveratrol	Respiratory chain/F_0F_1-ATP synthetase	[22]
17-Estradiol	Respiratory chain/F_0F_1-ATP synthetase	[22]
Apoptolidin	Respiratory chain/F_0F_1-ATP synthetase	[24]
Oligomycin	Respiratory chain/F_0F_1-ATP synthetase	[20]
Azelaic acid	Respiratory chain/oxidoreductase	[39]
2-ME	SOD activity	[27]
Genasense	Bcl-2 synthesis	[44]
HA14-1	Bcl-2 interaction	[45]
MKT-077	PTP	[48]
Cyclosporine A	PTP/cyclophilin D	[52,53]
Au(I)–carbene complexes	PTP	[55]
Sophoranone	PTP	[56]
F16	PTP	[57]
Betulinic acid	PTP/ANT	[60]
Lonidamine	PTP/ANT	[61]
Arsenic trioxide	PTP/ANT	[63]
	PTP/VDAC	[64]
	Respiratory chain	[65]
CD437	PTP/ANT	[62]
Ro5-4864	PTP/PBR	[68]
PK11195	PTP/PBR	[69]
Imexon	PTP/$\Delta\varphi$	[72]
Diazoxide	Potassium channel opener	[30,33]
EMD-60480 and EMD-57970	Potassium channel opener	[30]
Cromakalim	Potassium channel opener	[30]
Minoxidil	Potassium channel opener	[32]
Levosimendan	Potassium channel opener	[36]
NS1619	Potassium channel opener	[37]
NS004	Potassium channel opener	[37]
Dequalinium	Potassium channel blocker	[32]
Amiodarone	Potassium channel blocker	[32]

ANT; Adenine Nucleotide Translocase; PRB: Peripheral benzodiazepine receptor; PTP: Permeability Transition Pore; VDAC: Voltage-dependent anion channel.

mitochondria. Whatever be the degree of specificity, a determinant implication of mitochondria in the anti-cancer activity of all these molecules can be invoked. These observations legitimize the search for mitochondria-targeted anti-cancer compounds, all the more than, at least in theory; the direct targeting mitochondria may overcome the resistance mechanism encountered with conventional cytotoxic drug. Efforts are now directed toward the identification of ''mitochondriophilic'' molecules with the goal to identify novel anti-cancer agents. In our agitated world, certain wars are dictated by the privileged access to energy sites. The same picture can be applied to the war on cancer: taking control over mitochondria, the ''power houses of the cell'' certainly represents a desirable achievement but this is not without risk for the physiology of normal cells. Indeed, mitochondrial distress appears also as a leading cause of cell death in neurodegeneration [75]. Therefore, due to the frequent implication of mitochondria in neurodegenerative disorders, the impact of mitochondria-targeted anti-cancer agents on the central nervous system will certainly require a special attention.

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