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MINI REVIEW

Mitochondria-mediated ATP depletion by anti-cancer agents of the jasmonate family

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Abstract Jasmonates are plant stress hormones that induce suppression of proliferation and death in cancer cells, while being selectively inactive towards non-transformed cells. Jasmonates can overcome apoptotic blocks and exert cytotoxic effects on drug-resistant cells expressing p53 mutations. Jasmonates induce a rapid depletion of ATP in cancer cells. Indeed, this steep drop occurs when no signs of cell death are detectable yet. Experiments using modulators of ATP synthesis via glycolysis or oxidative phosphorylation suggest that the latter is the pathway suppressed by jasmonates. Consequently, the direct effects of jasmonates on mitochondria were evaluated. Jasmonates induced cytochrome c release and swelling in mitochondria isolated from cancer cells but not from normal ones. Thus, the selectivity of jasmonates against cancer cells is rooted at the mitochondrial level, and probably exploits differences between mitochondria from normal versus cancer cells. These findings position jasmonates as promising anti-cancer drugs acting via energetic depletion in neoplastic cells.

Keywords Cancer · Jasmonate · Plant · Energy · Glycolysis

Jasmonates as anti-cancer agents

Jasmonates are plant stress hormones. Before describing their newly-discovered anti-cancer activities, we will mention another plant stress hormone that has been studied for many years, i.e., salicylate. Salicylic acid and its synthetic derivative—acetyl salicylic acid, i.e., aspirin, have been studied as potential anti-cancer agents. Salicylate suppressed the proliferation of various types of cancer cells, including lymphoblastic leukemia, prostate, breast and melanoma human cancer cells (Fingrut and Flescher, 2002, Sotiriou et al., 1999). In addition, salicylate induced apoptosis in human myeloid leukemia cell lines (Klampfer et al., 1999), colorectal cancer cells (Elder et al., 1996, Lee et al., 2003), gastric cancer cells (Chung et al., 2003), and human glioblastoma cells (Amin et al., 2003). The synthetic salicylate aspirin suppressed the proliferation of metastatic murine melanoma cells and human melanoma cells (Ordan et al., 2003), human prostate cancer cell lines (Rotem et al., 2000), and colon cancer cells (Ara and Teicher, 1996; Fulton, 1987; Hanif et al., 1996; Shiff et al., 1996). Both natural and synthetic salicylates induced apoptosis in chronic lymphocytic leukemia (CLL) cells (Bellosillo et al., 1998). Recently, dietary salicylic acid and aspirin inhibited rat mammary carcinogenesis (Ghezzo et al., 2005).

In light of the above, we investigated the anti-cancer potential of another major plant stress hormone family—jasmonates. The basis for this comparison is based solely on their physiological roles since in plants, jasmonates and salicylate share function but not structure. Naturally-occurring jasmonates include several molecular species (Fig. 1A depicts the structures of three that have been studied as anti-cancer agents). Neoplastic cell lines, representing major solid tumors and hematogenic cancers, have been studied as targets for methyl jasmonate (MJ) action. A wide spectrum of malignancies, including three of the most important human cancers—prostate, breast and lung (Fingrut and Flescher, 2002; Kim et al., 2004), exhibited sensitivity to the cytotoxic effects of MJ. These cytotoxic effects include both apoptosis (determined biochemically and morphologically) and necrosis (Fingrut and Flescher, 2002). MJ induced a cytotoxic effect in cancer cells freshly isolated from blood samples

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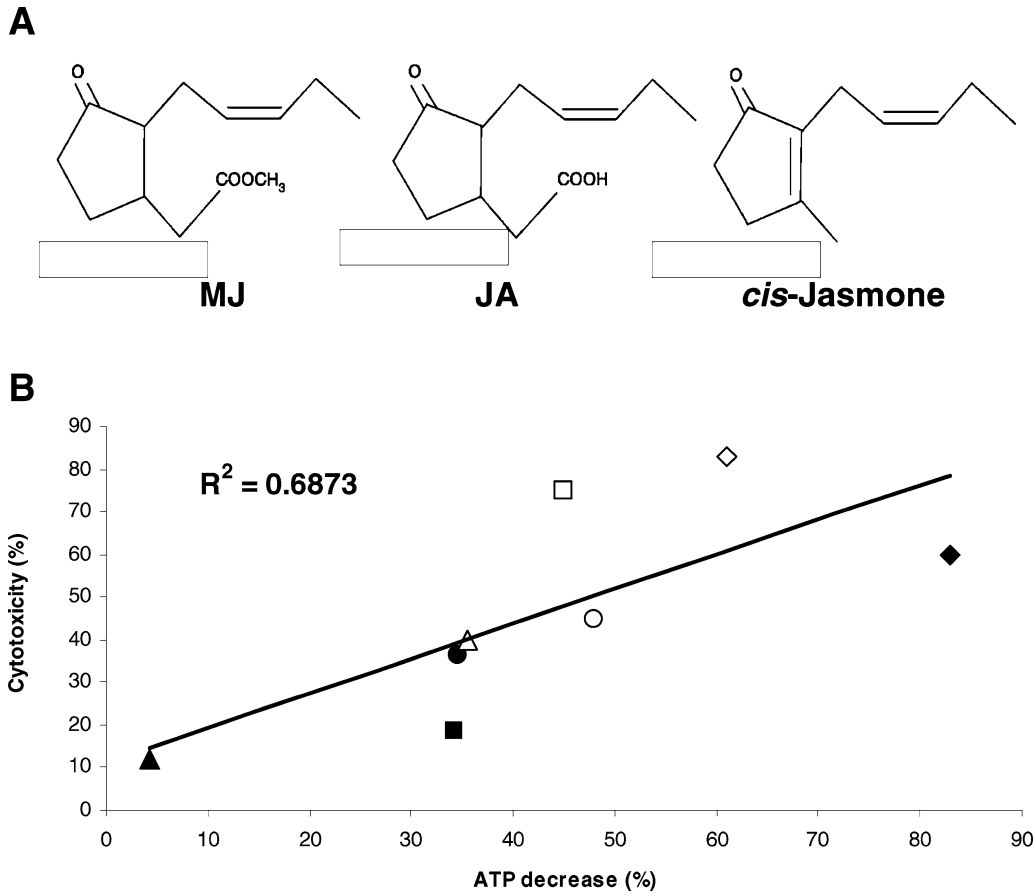

Fig. 1 A, Structure of jasmonates. Methyl jasmonate (MJ), jasmonic acid (JA), *cis*-Jasmone. B, Correlation between early ATP decrease and overnight cytotoxicity of MJ in different cell types. Cytotoxicity of 1 mM MJ was measured following overnight exposure using the Cell Proliferation Assay with XTT Reagent (Biological Industries, Beit Haemek, Israel). ATP decrease was determined following 15 minutes exposure to 3 mM MJ using the CellTiter-GloTM Luminescent Cell Viability Assay (Promega, Madison, WI, U.S.A.). Black triangle, peripheral blood lymphocytes freshly isolated from blood of healthy donors. Black square, murine colon carcinoma cell line CT-26. Black circle, murine lung carcinoma cell line D122. Empty triangle, human breast adenocarcinoma cell line MCF-7. Empty square, cells freshly taken from blood of chronic lymphocytic leukemia patients. Empty circle, murine melanoma cell line B16. Empty rhomb, human T cell lymphoblastic leukemia cell line Molt-4. Black rhomb, murine B cell leukemia cells BCL1. $N = 3$

drawn from CLL patients (Rotem et al., 2005). These patients suffered from B lymphocyte CLL and their blood cells had diverse responses to jasmonates ex-vivo. No correlation was found between the extent of the response with a given blood sample, and a number of clinical parameters including age, sex, stage of disease or medication. However, the percentage of leukemic cells within a given sample was in a direct and strong correlation with the degree of cytotoxicity exerted by MJ. This finding suggests a selective effect of MJ on leukemic cells. In order to test this hypothesis, the effect of MJ on the percentage of leukemic cells (expressing concomitantly two surface markers, CD19 and CD5) in blood samples from CLL patients was determined. Overnight incubation with MJ induced a dose-dependent decrease in the percentage of leukemic cells, supporting a preferential cytotoxic effect of MJ towards cancer cells (Flescher, 2005). Furthermore, jasmonates are significantly more cytotoxic towards a leukemic cell line (Molt-4) than towards lymphocytes isolated from blood drawn from healthy volunteers (Fingrut and Flescher, 2002). Thus, jasmonates exhibit an essential attribute of a potential anti-cancer drug, i.e., selectivity towards transformed cells.

Another desirable characteristic of an anti-cancer agent is its ability to act against drug-resistant cells. A common set of mutations that form the basis of chemo- and radioresistance in numerous human tumors are those occurring in the p53 tumor suppressor gene. In order to evaluate the susceptibility of drug resistant cells to jasmonates, the effects of jasmonates towards a pair of B lymphoma clones of the same line were investigated: one expressing wild type p53 and one expressing mutant p53. These clones differ drastically in their response to the cytotoxic drug bleomycin and the radiomimetic neocarzinostatin (NCS), i.e., the mutant p53-expressing clone is by far less susceptible to these agents (Fingrut et al., 2005; Flescher, 2007). In contrast, jasmonates were equally active against either clone. Interestingly, while

MJ induced mostly apoptotic death in the wild type p53-expressing cells, it induced necrotic death in the mutant p53-expressing cells (Fingrut et al., 2005; Flescher, 2007). Thus, jasmonates can circumvent the resistance of mutant p53-expressing cells towards chemotherapy by inducing a non-apoptotic mode of cell death.

In addition to *in vitro* studies, MJ was tested in a syngeneic mouse model of T lymphoma (EL-4). Administration of MJ *per os* daily increased significantly the survival of the lymphoma-bearing C57BL mice (Fingrut and Flescher, 2002). Thus, MJ was shown to suppress the growth of cancer cells *in vivo* as well as *in vitro*.

As mentioned, the activity of several natural jasmonates has been assessed in anti-cancer systems. MJ has been found to be superior to jasmonic acid (JA) in terms of cytotoxicity and caspase 3 activation (a marker of apoptosis). In accordance, the sensitivity of two prostate cancer cell lines was found to be in the following order: MJ>cis-Jasmone>JA (Samaila et al., 2004).

Jasmonates perturb the bio-energetic homeostasis in cancer cells

The vital role played by ATP has been demonstrated in various types of cells, both normal and neoplastic. The two major sources of cellular ATP, oxidative phosphorylation and glycolysis, as well as various mechanisms of ATP consumption, e.g., over-activation of poly(ADP-ribose) polymerase (PARP), determine the steady state levels of ATP. ATP depletion can result in different settings in either necrosis or apoptosis. Some examples highlighting these general concepts are hereby provided. The neurotoxin MPTP induced cell death, measured as LDH release, in neuroblastoma X glioma hybrid NG 108–15 cells. A drastic depletion in cell ATP content occurred prior to cell death and both phenomena were reduced by the presence of high levels of glucose in the medium, supporting higher rates of glycolysis-mediated ATP biosynthesis (Kutty et al., 1991). PARP over-activation following a cellular insult can lead to cell death caused by depletion of NAD and ATP. For instance, a study in mouse fibroblasts has demonstrated that PARP activation is an active trigger of necrosis (Ha and Snyder, 1999). Induction of oxidative stress in cells from the plant Arabidopsis caused increased hydrogen peroxide production, mitochondrial damage, cytochrome c release, ATP depletion and cell death (Tiwari et al., 2002). Exposure of embryonic rat cortical neurons to hydrogen peroxide induced ATP depletion and cell death by either necrosis or apoptosis (Aito et al., 2002). In the neonatal lamb ductus arteriosus, cell death is associated primarily with ATP depletion, and increased glycolytic capacity supports tolerance to hypoxia (Levin et al., 2005). Neutrophil apoptosis, occurring after these phagocytes perform their function, was reduced by increasing the levels of extra-cellular glucose. Under these conditions ATP levels rose significantly suggesting that the anti-apoptotic effect of high glucose concentration is mediated by maintenance of the intra-cellular ATP concentration (Healy et al., 2002). In light of the above we decided to investigate the possibility that the cytotoxic ability of jasmonates is related to perturbation of cellular energetic homeostasis.

MJ induced a drop in ATP cellular levels within 15 minutes, hours before any sign of cytotoxic effect could be recorded, in a variety of cancer cell types including leukemic cells obtained freshly from the blood of CLL patients. Indeed, we found a positive correlation between the susceptibility of a given cell type to the cytotoxic effect of MJ and the degree of ATP depletion induced in that cell (Fig. 1B). This correlation suggests the possibility of predicting the extent to which a given cell would be susceptible to jasmonates based on a very fast assay. Furthermore, normal lymphocytes which were practically resistant to MJ in terms of cell death, showed also lack of response in terms of ATP levels. Thus, it was hypothesized that jasmonates induce cancer cell death via a pathway involving ATP depletion. A specific tumor model was studied in this context. Murine B lymphoma cells were subjected to treatment with MJ. MJ induced a rapid time- and dose-dependent decrease in cellular ATP levels in both p53 wild type and mutant B lymphoma cells (Fingrut et al., 2005). Next, we investigated the mechanism by which MJ induces ATP depletion, i.e., what is the relative role of glycolysis versus oxidative phosphorylation in generating ATP in this model? Cells were pretreated with oligomycin (OM) (Zong et al., 2004; Lyamzaev et al., 2004) or with 2-deoxyglucose (DOG) (Lyamzaev et al., 2004) before treatment with MJ. OM inhibits oxidative phosphorylation by inhibiting mitochondrial ATP synthase (Salomon et al., 2000). DOG is an inhibitor of glycolysis (Maschek et al., 2004). Each of these inhibitors by itself induced only a moderate decrease in ATP levels suggesting that when either glycolysis or oxidative phosphorylation is inhibited there can be partial compensation by the other metabolic pathway. Combinations of MJ with the inhibitors were tested next. Pre-incubation with OM did not increase ATP depletion induced by MJ. It thus appears that MJ and OM act on the same ATP biosynthetic source, namely, the mitochondria; and that MJ perturbs these organelles to an extent that renders the OM effect irrelevant. On the other hand, inhibition of glycolysis (by DOG) enhanced significantly the effect of MJ on ATP levels, yielding a drastic depletion in cellular ATP levels. The flip side of the latter experimental approach (namely, inhibition of specific synthetic pathways) is to modulate ATP synthesis by controlling the levels of the relevant substrates. High glucose levels protected the B lymphoma cells from MJ induced ATP depletion while high levels of pyruvate did not. These results suggest again that

in the presence of MJ, mitochondria are unable to utilize pyruvate in order to generate ATP via oxidative phosphorylation. Finally, decreased ATP depletion, in culture medium containing high levels of glucose, correlated with decreased cytotoxicity of MJ (Fingrut et al., 2005). Thus, our results support our hypothesis that ATP depletion is a major mechanism of MJ-induced cytotoxicity. Furthermore, oxidative phosphorylation in the mitochondria appears to be the target of MJ-induced bio-energetic perturbation. Consequently, we studied direct effects of jasmonates on mitochondria isolated from cancer cells.

Our initial approach to the issue of mitochondrial involvement in jasmonate-induced cancer cell death was to evaluate perturbation of mitochondrial membrane potential. MJ, cis-Jasmone and JA induced membrane depolarization in Molt-4 cells (Rotem et al., 2005) and their relative potency correlated with their respective cytotoxic effects on these cells (Fingrut and Flescher, 2002). Further analysis focused on the potent jasmonate derivative MJ. Many cytotoxic agents, among them various chemotherapeutic drugs, induce cell death via mechanisms involving mitochondria. Nevertheless, the common scenario involves engagement of death receptors or some cellular stress causing DNA damage. The effects of these early events converge at the mitochondrial level and result eventually in cell death. Thus, determination of mitochondrial membrane depolarization in intact cells does not necessarily imply that the jasmonates act directly upon mitochondria. Therefore, mitochondria were isolated from human Molt-4 leukemia and Hep 3B hepatoma cells, and their fate in the presence of MJ was determined. In order to evaluate permeability transition in isolated mitochondria, we subjected these organelles to MJ treatment and measured two characteristic phenomena: release of cytochrome c and mitochondrial swelling. The permeability transition pore complex (PTPC) regulates movement of compounds across the mitochondrial membrane. Abnormally long opening of this pore can be associated with cytochrome c escape into the cytosol, initiating a cascade which culminates in cell death. MJ induced the release of cytochrome c from mitochondria isolated from Molt-4 and from Hep 3B cells, in a time-dependent manner. Thus, our findings indicate that MJ affects directly mitochondria isolated from cancer cells and induces permeability transition. On the other hand, MJ did not induce release of cytochrome c from mitochondria isolated from normal lymphocytes, in agreement with the selective cytotoxic effect of MJ against transformed cells (Fingrut and Flescher, 2002; Rotem et al., 2005). Furthermore, in order to assess the involvement of PTPC in MJ-induced permeability transition, we employed inhibitors of the PTPC opening which act via interaction with proteins in the mitochondrial inner membrane: cyclosporin A (CSA) and bongkrekic acid (BA) (Rotem et al., 2005). These inhibitors can inhibit the cytotoxic activity of agents that exert their effect via opening of the PTPC. Notably, the MJ-induced release of cytochrome c from mitochondria isolated from cancer cells was inhibited by CSA and BA suggesting that the mitochondrial permeability transition induced by MJ is PTPC-mediated (Rotem et al., 2005). In addition, MJ induced mitochondrial swelling, and CSA and BA prevented this effect of MJ. In contrast, MJ did not induce swelling in mitochondria isolated from 3T3 human fibroblasts. Since these cells are immortal but non-transformed, these results suggest again that jasmonates act selectively on mitochondria isolated from transformed cells. In summary, determination of mitochondrial permeability transition by both cytochrome c release and mitochondrial swelling assays indicates that MJ affects mitochondria isolated from transformed cells directly, in a PTPC-mediated manner (Rotem et al., 2005). While the effects of MJ on isolated mitochondria were significant, they could theoretically be irrelevant to the situation in whole cells. To rule out this possibility, we determined the effects of PTPC inhibitors on MJ-induced mitochondrial perturbation and cytotoxicity in intact human cancer cells. Both CSA and BA inhibited MJ-induced mitochondrial membrane depolarization in Molt-4 cells. In addition, CSA and BA inhibited significantly the cytotoxic effects of MJ towards Molt-4 and Hep 3B cells (Rotem et al., 2005).

Having shown the toxic effects of MJ against mitochondria isolated from human cancer cell lines, we evaluated these effects in ex-vivo cells freshly taken from CLL patients. The latter cells probably represent better the actual situation in the patient. Jasmonates induced membrane depolarization in intact leukemic cells from CLL patients. Experiments with mitochondria isolated from lymphocytes obtained from the blood of CLL patients showed that MJ induced mitochondrial swelling and release of cytochrome c from the mitochondria, similar to its effects on mitochondria from cancer cell lines. Thus, mitochondria isolated from cell lines bear the characteristics of mitochondria isolated from leukemic cells taken freshly from CLL patients, at least as far as the effects of MJ are concerned. On the other hand, mitochondria isolated from normal lymphocytes did not swell in response to MJ, supporting again our position that MJ has a selective effect on mitochondria isolated from cancer cells. To summarize the above, jasmonates are capable of perturbing directly and selectively mitochondria from cancer cells, thereby depleting their ATP generation capacity, resulting in cell death (Rotem et al., 2005). This proposed mechanism of action fits the findings that MJ-induced cytotoxicity is transcription- and translation-independent (Rotem et al., 2003).

An essential issue that needs to be addressed is the basis for the selective effect on mitochondria from transformed cells. Several findings suggest that the composition and function of mitochondria in cancer cells and normal cells differ. These include a higher mitochondrial membrane

potential, possible modulation of the expression of PTPC components, and enhanced rates of ATP generation through glycolysis rather than through oxidative phosphorylation (a phenomenon known as the Warburg effect) in cancer cells (Warburg et al., 1930; Pedersen, 1978; Chen, 1988; Dang and Semenza, 1999; Debatin et al., 2002). Studies of samples freshly taken from human tumors suggest that these cancers exhibit abnormalities in their mitochondrial energy generation capacity. Liver carcinomas exhibit depletion of cellular mitochondrial contents. Tumors originating from colon, kidney, breast, stomach, oesophagus and lung, express significantly reduced levels of the beta-catalytic subunit of the mitochondrial H^+-ATP synthase (Cuezva et al., 2002; Isidoro et al., 2004). In the context of potential clinical application of these findings, one must assume that jasmonates can reach normal cells as well. However, their effects on mitochondria from cancer cells should be different. The difference may be related to PTPC components that jasmonates can directly interact with. Also, the defective ability of mitochondria in cancer cells to generate ATP to begin with, may turn these organelles into the weak point of the cells. Given the central role mitochondrial membrane permeabilization plays in apoptosis, the concept of apoptogenic compounds acting directly on mitochondria has recently become a focus of intense investigation (Brenner and Grimm, 2006; Galluzzi et al., 2006).

The effects of MJ on A549 human adenocarcinoma cells were analyzed in whole cell systems and effects of mitochondria-related parameters were recorded (Kim et al., 2004). Levels of the pro-apoptotic proteins Bax and Bcl-X_S were increased while those of the anti-apoptotic Bcl-X_L and Bcl-2 remained unchanged. Given that Bcl-2 family proteins act in mitochondria, these results suggest that the aforementioned pro-apoptotic proteins mediate MJ-induced mitochondrial perturbation resulting in apoptosis. Indeed, MJ induced activation of caspase-9 (Kim et al., 2004). Furthermore, MJ treatment enhanced the levels of hydrogen peroxide and mitochondrial reactive oxygen species in A549 cells. Thus, Kim et al. propose that MJ induces apoptosis in these cells by perturbing their mitochondria through the action of pro-apoptotic proteins belonging to the Bcl-2 family, and that oxygen intermediates are involved in this process (Kim et al., 2004).

Plant-derived anti-cancer compounds affecting cellular bioenergetics

Jasmonate as a plant-derived agent capable of perturbing cancer cell bio-energetics needs to be put into a wider perspective of a series of plant products exhibiting activities with shared characteristics. In general, anti-cancer effects of plant compounds and extracts can be at the preventive as well as the therapeutic level. In fact, a preventive effect may actually be a direct cytotoxic activity on a pre-malignant cell. In a chemopreventive model, the plant-derived rotenoid—deguelin, inhibited the activation of ornithine decarboxylase (ODC) by TPA. Further analysis exhibited that deguelin inhibited mitochondrial NADH dehydrogenase, complex I of the respiratory chain, and this correlated with a rapid depletion of ATP. These results suggest that deguelin denies the cell its energy requirements during ODC induction, resulting in an inhibition of the transformation process (Gerhäuser et al., 1997). Thus, plant–derived agents can exert chemopreventive effects via energetic depletion resulting from oxidative phosphorylation inhibition.

In rats bearing carcinogen-induced hepatocellular carcinoma, the activities of plasma and liver glycolytic enzymes (hexokinase, phosphoglucoisomerase and aldolase) were increased, while that of glucose-6-phosphatase was decreased. The ethanol extract of *Terminalia arjuna* (a tropical woody tree), that was found to be useful in cancer treatment and can suppress the growth of various cell lines, reversed these abnormalities when administered orally. Thus, the *T. arjuna* extract suppresses glycolytic energy metabolism, thereby inhibiting cancer growth (Sivalokanathan et al., 2005). Studies in mammary carcinoma-bearing rats show a rise in glycolytic enzymes and fall in gluconeogenic enzymes (Arathi and Sachdanandam, 2003), similar to the above-mentioned findings in hepatocellular carcinoma. In addition, the mammary tumor model exhibits a significant decrease in mitochondrial enzymes (isocitrate dehydrogenase, NADH dehydrogenase, cytochrome c oxidase, etc.). When the tumor-bearing rats were administered *Semecarpus anacardium* nut milk extract (used in ethnic medicine to treat cancer), both the glycolysis and mitochondria-related enzymatic abnormalities were reversed. Thus, an anti-cancer preparation normalized the balance between the two major cellular sources of ATP. It still remains to be determined whether it is the balance and/or the net cellular concentration of ATP, that is important for the anti-cancer activity, (Arathi and Sachdanandam, 2003). In a different mechanism, avicins (triterpenoid electrophilic metabolite molecules from *Acacia victoriae*) induce apoptosis in leukemic cells by targeting the mitochondria and lowering cellular energy metabolism (Gaikwad et al., 2005). Yet another plant-derived agent (echitamine chloride, an indole alkaloid extracted from the bark of *Alstonia scholaris*), induced in sarcoma cells suppression of both mitochondrial oxygen consumption and of glycolysis (Saraswathi et al., 1998). An attempt to formulate a comprehensive view of the studies described with various plant-derived agents suggests that in each case at least one of the cellular ATP sources is inhibited, and sometimes both are. In a rational manner, the field has evolved to the most straightforward experimental approach towards energetic perturbation, i.e., elimination of cellular ATP, rather than prevention of its synthesis.

As mentioned above, PARP over-activation leads to NAD and ATP consumption, resulting in either necrosis (Zong et al., 2004) or apoptosis (Bentle et al., 2006). Indeed, the plant toxin ricin induces apoptotic death of U937 cells by decreasing intracellular NAD(+) and ATP levels via PARP activation (Komatsu et al., 2000). In an attempt to eliminate ATP directly, Frydman et al. exploited the affinity of polyamine macrocycles for ATP as well as their ATP-ase mimicry. They synthesized a series of analogs to the polyamine macrocycle alkaloids from *Albizia amara*, and found that these compounds are cytotoxic towards prostate cancer cells, in correlation with their efficacy in depleting endogenous ATP levels (Frydman et al., 2004). If and when chemicals with ATP-ase activity can be directed specifically to tumor cells, they may well turn out to be very promising novel anti-cancer agents based on the principle of energetic perturbation.

Conclusion

Differences between normal and cancer cells, in terms of their bio-energetic metabolism, have been known for many years. More pertinent to this article, various differences in mitochondrial structure and function have been documented. It is therefore only natural, and probably overdue, that attempts are made to discover ways of exploiting these differences in order to interfere specifically with the growth and viability of cancer cells. We have discovered that jasmonates have anti-cancer activities in vitro and in vivo. Our findings suggest that jasmonates affect mitochondria in cancer cells directly and selectively, and induce ATP depletion as well as mitochondrial permeability transition mediated via opening of the PTPC (Fig. 2). Since many of the mutations endowing cancer cells with drug resistance are

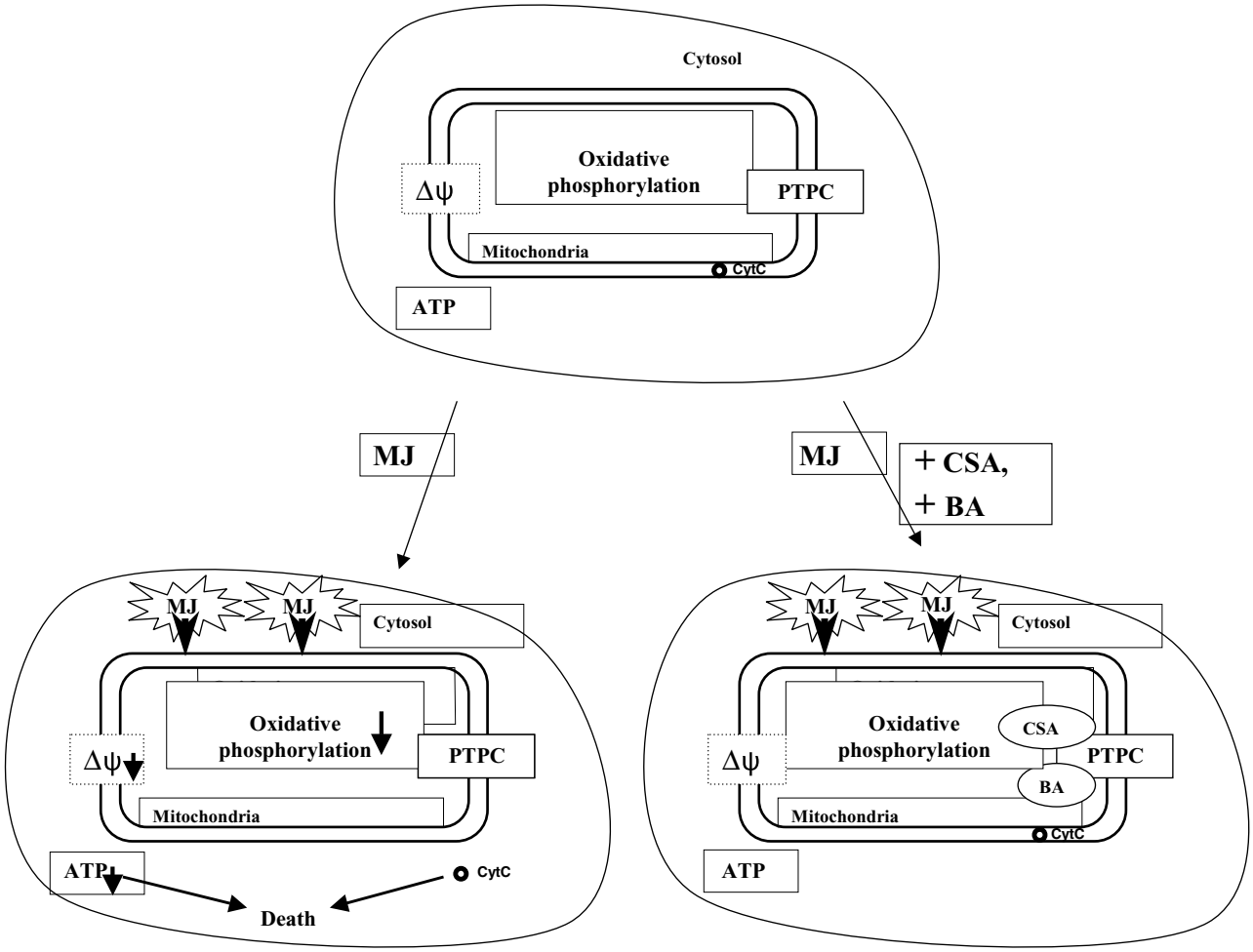

Fig. 2 MJ-induced mitochondrial perturbation and ATP depletion in cancer cells. MJ interacts with the mitochondria at an unknown site, leading to cell death. Lower left – MJ induces release of cytochrome c (CytC, black donut) from the inter-membrane space into the cytosol, a decrease in mitochondrial membrane potential, inhibition of oxidative phosphorylation and a drop in cellular ATP levels, resulting in apoptosis. Lower right – inhibitors of the PTPC opening, cyclosporine A (CSA), and bongkrekic acid (BA), inhibit the mitochondrial damage by preventing the PTPC opening. CSA and BA bind to and inhibit components of the PTPC located in the mitochondrial inner membrane (cyclophilin D and adenine nucleotide translocator, respectively)

pre-mitochondrial, compounds affecting mitochondria directly can bypass such apoptotic blocks and exhibit efficacy towards chemoresistant tumors. Discovery of the mitochondrial molecular target/s of jasmonates should pave the road towards rational design of novel jasmonate-based anti-cancer drugs.

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