Methyl jasmonate binds to and detaches mitochondria-bound hexokinase.


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Cellular bio-energetic metabolism and mitochondria are recognized as potential targets for anticancer agents, due to the numerous relevant peculiarities cancer cells exhibit. Jasmonates are anticancer agents that interact directly with mitochondria. The aim of this study was to identify mitochondrial molecular targets of jasmonates. We report that jasmonates bind to hexokinase and detach it from the mitochondria and its mitochondrial anchor—the voltage-dependent anion channel (VDAC), as judged by hexokinase immunochemical and activity determinations, surface plasmon resonance analysis and planar lipid bilayer VDAC-activity analysis. Furthermore, the susceptibility of cancer cells and mitochondria to jasmonates is dependent on the expression of hexokinase, evaluated using hexokinase-overexpressing transfectants and its mitochondrial association. Many types of cancer cells exhibit overexpression of the key glycolytic enzyme, hexokinase, and its excessive binding to mitochondria. These characteristics are considered to play a pivotal role in cancer cell growth rate and survival. Thus, our findings provide an explanation for the selective effects of jasmonates on cancer cells. Most importantly, this is the first demonstration of a cytotoxic mechanism based on direct interaction between an anticancer agent and hexokinase. The proposed mechanism can serve to guide development of a new selective approach for cancer therapy.

PMID: 18408762

Methyl jasmonate: a plant stress hormone as an anti-cancer drug.


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Jasmonates act as signal transduction intermediates when plants are subjected to environmental stresses such as UV radiation, osmotic shock and heat. In the past few years several groups have reported that jasmonates exhibit anti-cancer activity in vitro and in vivo and induce growth inhibition in cancer cells, while leaving the non-transformed cells intact. Recently, jasmonates were also discovered to have cytotoxic effects towards metastatic melanoma both in vitro and in vivo. Three mechanisms of action have been proposed to explain this anti-cancer activity. The bio-energetic mechanism—jasmonates induce severe ATP depletion in cancer cells via mitochondrial perturbation. Furthermore, methyl jasmonate (MJ) has the ability to detach hexokinase from the mitochondria. Second, jasmonates induce re-differentiation in human myeloid leukemia cells via mitogen-activated protein kinase (MAPK) activity and were found to act similar to the cytokinin isopentenyladenine (IPA). Third, jasmonates induce apoptosis in lung carcinoma cells via the generation of hydrogen peroxide, and pro-apoptotic proteins of the Bcl-2 family. Combination of MJ with the glycolysis inhibitor 2-deoxy-d-glucose (2DG) and with four conventional chemotherapeutic drugs resulted in super-additive cytotoxic effects on several types of cancer cells. Finally, jasmonates have the ability to induce death in spite of drug-resistance conferred by either p53 mutation or P-glycoprotein (P-gp) over-expression. In summary, the jasmonates are anti-cancer agents that exhibit selective cytotoxicity towards cancer cells, and thus present hope for the development of cancer therapeutics.

PMID: 19660769

Jasmonates—a new family of anti-cancer agents.


Since salicylate, a plant stress hormone, suppresses the growth of various types of cancer cells, it was deemed of interest to investigate whether the jasmonate family of plant stress hormones is endowed with anti-cancer activities. Cell lines representing a wide spectrum of malignancies, including prostate, breast and lung, exhibit sensitivity to the cytotoxic effects of methyl jasmonate (MJ). Jasmonates induced death in leukemic cells isolated from the blood of chronic lymphocytic leukemia (CLL) patients and increased significantly the survival of lymphoma-bearing mice. Among the naturally occurring jasmonates, MJ is the most active, while the synthetic methyl-4,5-didehydrojasmonate, was approximately 29-fold more active than MJ. The cytotoxic activity of MJ is independent of transcription and translation. Studies have suggested several mechanisms of action. It appears that while prolonged exposures to relatively low concentrations of jasmonates induce growth arrest and re-differentiation in myeloid leukemia cells, higher concentrations of MJ induce direct perturbation of cancer cell mitochondria, leading to the release of cytochrome c and eventual cell death. A most important characteristic of jasmonates is their ability to selectively kill cancer cells while sparing normal cells. Even within a mixed population of normal and leukemic cells derived from the blood of CLL patients, MJ killed preferentially the leukemic cells. In conclusion, jasmonates present a unique class of anti-cancer compounds which deserves continued research at the basic and pharmaceutical levels in order to yield novel chemotherapeutic agents against a range of neoplastic diseases.

PMID: 16162967

Jasmonates in cancer therapy.


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the Bcl-2 family. Several similarities between the effects of jasmonates on plant and cancer cells have been recorded, suggesting that additional analysis of jasmonate effects in plant cells may contribute to a deeper understanding of the anti-cancer actions of these compounds. Those similarities include: induction of cell death, suppression of proliferation and cell cycle arrest, MAPK induction, ROS generation, and enhancement of heat-shock proteins (HSP) expression. Finally, jasmonates can induce death in drug-resistant cells. The drug resistance was conferred by either p53 mutation or P-glycoprotein (P-gp) over-expression. In summary, the jasmonate family of novel anti-cancer agents presents new hope for the development of cancer therapeutics, which should attract further scientific and pharmaceutical interest.

PMID: 16600475