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Cooperative cytotoxicity of methyl jasmonate with anti-cancer drugs and 2-deoxy-D-glucose

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Abstract

The anti-cancer agent methyl jasmonate (MJ) acts in vitro and in vivo against various cancer cell lines, as well as leukemic cells from chronic lymphocytic leukemia (CLL) patients. Given the importance of multi-agent combinations in cancer chemotherapy, the purpose of this study was to identify super-additive combinations of MJ and currently-available chemotherapeutic drugs. We identified such cooperative effects in six cell lines arising from different major types of malignancies, i.e., breast, lung, prostate and pancreas carcinomas as well as leukemia. The chemotherapeutic drugs tested were adriamycin, taxol, BCNU and cisplatin. For instance, MJ exhibited strong cooperative effects with BCNU in MIA PaCa-2 pancreatic carcinoma cells. Furthermore, MJ enhanced significantly ($pV = 0.028$) the anti-leukemic effect of adriamycin in vivo, in a CLL mouse model. Finally, MJ cooperated with the glycolysis inhibitor 2-deoxy-D-glucose in inducing death of several types of carcinoma cells. We conclude that administration of MJ with common chemotherapeutic drugs and glycolysis inhibitors bears a promise for effective anti-cancer therapy.
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Keywords: Jasmonate; Chemotherapy; Cooperation; 2-Deoxy-D-glucose; ATP; BCL1 leukemia

1. Introduction

We discovered that a group of plant stress hormones named jasmonates possess anticancer activities *in vitro* and *in vivo* [1]. Methyl Jasmonate (MJ) increased significantly the survival of lymphoma-bearing mice [1] and induced death in human leukemia, prostate, breast and melanoma cell lines, as well as in leukemic cells from chronic lymphocytic leukemia (CLL) patients [2,3]. On the other hand, peripheral blood erythrocytes [4], normal lymphocytes [1,2] and human sperm cells (E. Flescher, personal communication) were found to be resistant to jasmonate cytotoxicity. These results strongly support the conclusion that jasmonates target specifically transformed cells. Previously, we analyzed the jasmonate-induced cellular death process in Molt-4 human lymphoblastic leukemia cells and found that these plant compounds are capable of inducing both necrotic and apoptotic death [1]. Furthermore, we determined that jasmonates are capable of killing cancer cells in a manner independent of cellular mRNA transcription, protein translation [5], and p53 expression [6].

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Recent studies have analyzed the mechanism through which jasmonates induce cell death. Mitochondria were found to play a pivotal role in the mechanism of action of jasmonates. Indeed, jasmonates act directly on mitochondria, resulting in cell death [2]. Jasmonates induced mitochondrial membrane depolarization and cytochrome *c* release in intact cancer cells [2]. More importantly, MJ induced swelling and cytochrome *c* release in mitochondria isolated from human leukemia and hepatoma cell lines, as well as leukemic cells from CLL patients [2]. However, jasmonates did not induce cytochrome *c* release or swelling in mitochondria isolated from normal lymphocytes. It thus appears that the difference between the normal and cancer cells exists at the mitochondrial level. Interestingly, jasmonates did not induce swelling in mitochondria isolated from immortal, but non-transformed, 3T3 mouse fibroblasts [2], suggesting that neoplastic transformation renders the mitochondria susceptible to jasmonates. Thus, MJ has direct mitochondriotoxic effects, strongly suggesting that mitochondria are target organelles of jasmonates. In support of this contention, inhibitors of the opening of the mitochondrial permeability transition pore complex (PTPC, a pore mediating mitochondrial perturbation resulting in cell death) reduced significantly the toxic effects of MJ on cancer cells and on mitochondria isolated from these cells. These studies [2] show that jasmonates kill cancer cells in a PTPC-dependent manner. The direct effect of jasmonates on mitochondria should endow them with the ability to bypass pre-mitochondrial anti-apoptotic mutations, thereby making this class of anti-cancer agents potentially active against a variety of drug-resistant tumors.

In accordance with principles for selecting agents for use in combination chemotherapy regimens, drugs with different mechanisms of action and with additive or synergistic cytotoxic effects on the tumor should be combined [7]. Multi-agent therapy has three important theoretical advantages over single-agent therapy. First, it can maximize cell kill while minimizing host toxicities by using agents with non-overlapping dose-limiting toxicities. Second, it may increase the range of drug activity against tumor cells with endogenous resistance to specific types of therapy. Finally, it may also prevent or slow the development of newly resistant tumor cells [7]. Virtually, almost all curative chemotherapy regimens for cancer employ multi-agent drug combinations [8]. Although ideal drug combinations would be those that are synergistically active against malignant cells without increased systemic toxicity, additive antitumor activity with favorable toxicity profile can also be clinically beneficial [9].

Since the research described in the present article revolves around combinations of jasmonates with various chemotherapeutic agents, we indicate below the mechanism of action of the relevant drugs. Chemotherapeutic agents can be classified by mechanism of action. The alkylating agents impair cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl and phosphate groups in biologically important molecules. The most important sites of alkylation are DNA, RNA and proteins. Alkylating agents depend on cell proliferation for activity but are not cell-cycle-phase-specific. Alkylating agents are classified according to their chemical structures and mechanisms of covalent bonding; this drug class includes the nitrogen mustards, nitrosoureas (BCNU) and platinum complexes (cisplatin) [7]. Taxanes are semisynthetic derivatives of extracted precursors from the needles of yew plants. These drugs have a novel 14-member ring, the taxane. Unlike the vinca alkaloids, which cause microtubular disassembly, the taxanes (e.g. taxol) promote microtubular assembly and stability, therefore blocking the cell cycle in mitosis [7]. Antitumor antibiotics like adriamycin intercalate DNA at guanine–cytosine and guanine–thymine sequences, resulting in spontaneous oxidation and formation of free oxygen radicals that cause strand breakage [7].

Recently, it has been shown using three *in vitro* models of simulated hypoxia [10–12], that cells under hypoxic conditions are more sensitive than cells under aerobic conditions to agents that inhibit glycolysis, such as 2-deoxy-D-glucose (2DG). Because a slowly proliferating tumor population can be selectively killed with glycolytic inhibitors, combining such agents with chemotherapeutic drugs, which target the rapidly dividing aerobic cells, should raise the overall efficacies of these treatments [10–12]. Indeed, the combination of 2DG and cisplatin is more effective than either agent alone when applied to various cell lines that are rapidly proliferating *in vitro* [13]. Similar *in vitro* synergism has been observed with the combination of 2DG and adriamycin (ADR) in MCF7 cells [14]. It has recently been found in our laboratory, that 2DG and MJ had an additive effect on ATP depletion in B-lymphoma cells expressing either wt or mutant p53 [6]. The basis for this additive effect is probably the inhibitory actions jasmonates and 2DG have on

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