Plant Signaling & Behavior 10:9, e1062199; September 2015; © 2015 Crown copyright

Methyl jasmonate and its potential in cancer therapy

Meng Zhang[1], Michael W Zhang[1], Lili Zhang[1], and Lingrui Zhang[2,*]

[1]College of Life Science and Agronomy; Zhoukou Normal University; Zhoukou, China; [2]Southern Crop Protection and Food Research; Agriculture and Agri-Food Canada; London, ON, Canada

Methyl jasmonate (MeJa) is a naturally occurring hydrophobic oxylipin phytohormone. Early findings obtained from cancer cell lines suggest that MeJa is endowed with anticancer capabilities. It has been recently proposed that MeJa represents a novel agent that exhibits direct and selective actions against tumor cells without affecting normal human cells. In a previous study, I reported that MeJa itself is enough to result in the dysfunction of mitochondria and chloroplasts, as well as to activate cell death program (apoptosis), in the normal protoplasts of *Arabidopsis thaliana*. Indeed, this also holds true for other living plant systems in which senescence, hypersensitive response and oxidative stress have been found under MeJa action. Therefore, in this addendum to my previous article, I would like to stress that much more attention should be paid to the potential effect(s) of MeJa, or its derivatives, on healthy cells and tissues before it is used for clinical anticancer drugs, whether being used alone or in combination with other agents.

Keywords: anticancer agent, apoptosis, cancer, cell death, methyl jasmonate

*Correspondence to: Lingrui Zhang; Email: zhanglingrui@gmail.com

Submitted: 06/03/2015

Accepted: 06/10/2015

http://dx.doi.org/10.1080/15592324.2015.1062199

Addendum to: Zhang L, Xing D. Methyl jasmonate induces production of reactive oxygen species and alterations in mitochondrial dynamics that precede photosynthetic dysfunction and subsequent cell death. Plant Cell Physiol 2008; 49:1092-111. DOI:10.1093/pcp/pcn086.

Methyl jasmonate (MeJa) is a lipid-derived endogenous hormone that plays crucial roles in both developmental processes and diverse defense responses in plants (**Fig. 1**). A host of studies have demonstrated that MeJa signaling is rapidly and effectively initiated upon pathogen or insect attack, as well as in response to elicitors such as chitins, oligosaccharides and oligogalaturonides.[1,2] In a sense of being widely accepted, pathogens with a biotrophic lifestyle are particularly sensitive to salicylic acid (SA) -mediated defenses, whereas necrotrophic pathogens and herbivorous insects are resisted through jasmonate, or its derivatives, -mediated defenses.[3] Although molecular mechanisms of MeJa action, as well as the antagonistic effects of MeJa and other defense hormones such as SA, on the modulation of plant immune signaling networks have been extensively studied,[3] the dynamic cellular events and signaling cascade profiles following the introduction of MeJa in a single living cell are largely unknown.

In 2008, I as a first author reported that the administration of exogenous MeJa triggers a time-dependent production of reactive oxygen species (ROS) which first accumulate in mitochondria, and subsequently in chloroplasts, in protoplasts of *Arabidopsis thaliana* (**Fig. 2**).[4] Moreover, MeJa treatment not only causes alterations of mitochondrial dynamics, including movement cessation, transmembrane potential loss, and morphological transition and swelling, but also distorts photosynthetic organelles.[4] The production of ROS and subsequent organelle dysfunction were shown to occur upstream of cell death and to be necessary components of cell death processes (**Fig. 2**).[4] In fact, Fingrut and Flescher have reported in 2002 that MeJa can induce apoptosis in human cancer cells, including Molt-4, SK-28, LNCaP, and MCF7.[5] They also demonstrated that MeJa is in contrast to another plant hormone, salicylic acid (SA), in terms of their effect on cancer cells, as the latter arrests the cell cycle and suppresses cell proliferation in each of the cell lines mentioned above.[5] They further showed that after treatment with MeJa, mice bearing EL-4 lymphoma can survive for significantly longer periods of time than untreated mice.[5] Other groups also showed that MeJA triggers apoptosis by not only inducing the expression of pro-apoptotic members of the Bcl-2, Bax and Bcl-XS

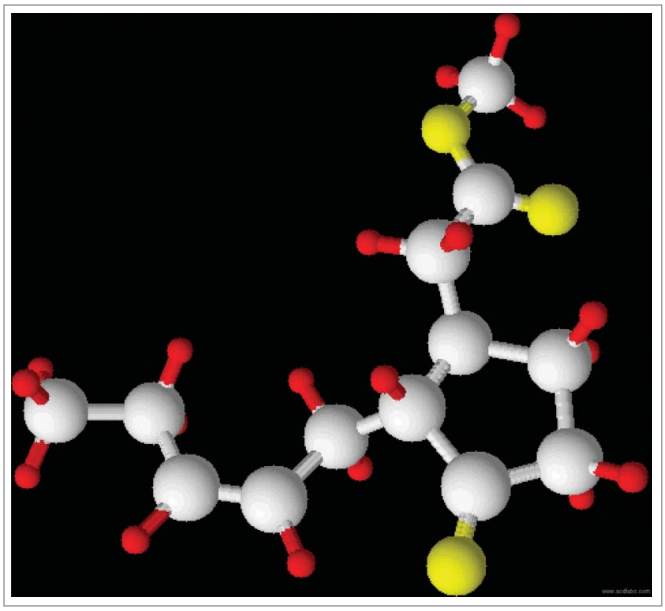

Figure 1. Chemical structure of methyl jasmonate (cyclopentaneaceticacid, 3-oxo-2-(2-penten-1-yl)-, methyl ester) is displayed as cartoon. The balls in yellow, white and red represent oxygen, carbon and hydrogen, respectively.

protein families, but also activating caspase-3 via mitochondria in a ROS-dependent manner in human cancer cells (**Fig. 2**), such as A549 human lung adenocarcinoma cells.[6,7] These data indicate that in both plant and human cells, mitochondria and ROS might hold a key role in MeJa signaling pathways, and that MeJa-induced cell death programs might be highly conserved (**Fig. 2**).[4,6,7]

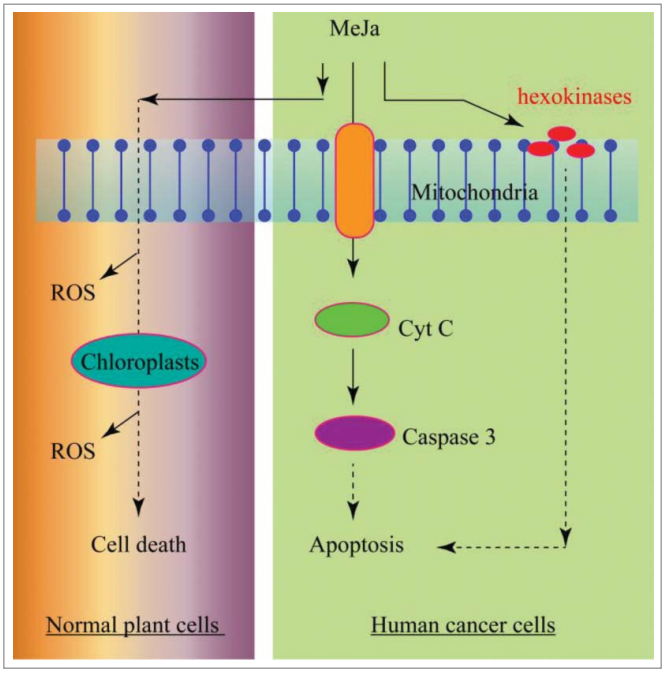

Figure 2. The actions of MeJa on plant cells (left panel) and human cancer cells (right panel). Besides the cell death, senescence, hypersensitive response and oxidative stress have also been found in many living plant systems under MeJa action. A more detailed explanation is given in text.

In fact, it has been proposed that mitochondria in cancer cells are the direct and specific target of MeJa action.[7] In view of its roles in the induction of suicide programs in cancer cell lines, and of its potential and promise as an anticancer drug, great efforts have been made to explore the molecular mechanisms of MeJa action(s) on cancer cells and mitochondria.[7-10] However, it still remains unclear why apoptosis programs are specifically activated by MeJa in cancer cells, but not in normal human cells. Even so, it has been overwhelmingly proposed that MeJa is a novel class of anticancer drugs that act directly and selectively against tumor cells both *in vitro* and *in vivo*, without affecting normal cells such as lymphocytes.[7-10] Although the susceptibility of cancer cells and mitochondria to MeJa was shown to be dependent on the evaluated expression of hexokinase,[10] a key hallmark of many types of cancer cells, the mechanisms underlying MeJa-induced detachment of hexokinase from mitochondria and subsequent apoptosis is yet to be known. Hexokinase II is the major form of hexokinase in cancer cells, however MeJa shows no specificity and selectivity in binding hexokinase I and hexokinase II in the mitochondria of cancer cells.[10] Moreover, it has been shown that only 80% of hexokinase II is associated with mitochondria.[11] Therefore, there is still a potential risk in the application of MeJa in clinical cancer therapies, especially considering the fact that hexokinase I and hexokinase II are also expressed in normal brain, kidney, heart and skeletal tissues.[12]

Without doubt, extensive investigation into the potential side effects of MeJa on normal human cells or animal models, and intensive examination of the selective effects (target molecules) of MeJa on cancer cells, are particularly urgent. This would not only assist in understanding the mysteries behind MeJa-induced apoptosis, but also provide us with a fact-based view that can serve to guide the further development of a novel class of selective MeJa-based anticancer approaches in clinical therapies.[7,9] Understanding the potential side effects of MeJa actions will increase our ability to foresee the clinical settings in which MeJa and its derivatives would be effective as anticancer agents. On the other hand, identifying the target

molecules with which MeJa interacts may allow for the rational design of more potent MeJa derivatives. Obviously, there is a long road ahead when considering that only hexokinase has been identified as a MeJa-binding protein thus far, both in plants and in animals.[10] In addition, an increasing body of evidence shows that MeJa is capable of driving senescence programs or hypersensitive response in a variety of experimental plant systems such as intact plants, plant explants, detached or attached leaves, suspension-cultured cells and protoplasts.[13-23] Therefore, it is reasonable to suggest that a comprehensive evaluation of MeJa actions should be carried out in human cell lines to examine the possible changes in aging programs and immune systems under MeJa treatment, although the inherent senescence programs and immune response systems are different from plants to human cells.

It has been 7 y since that paper was published in *Plant and Cell Physiology*. However, still today I have had a desire to write this addendum due to a concern about the unidentified effects of MeJa on healthy human cells. It is anticipated that through this addendum, increased attention will be paid to the possible side effects of MeJa. Also, I write this addendum to make a reply to the invitation made by Dr. Frantisek Baluska 7 y ago, as late thanks for his invitation that does not fade at all even after many years. When I contacted with him serval days ago, I got a rapid response, which is 'Yes, my invitation is still valid'. In fact, on that year I was not able to respond immediately due to a tough situation I met as a student who was stuck in the middle, helpless, due to an obligatory page charge, which will be revealed in detail in the near future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We are grateful to Jamie McNeil (Agriculture and Agri-Food Canada) for his suggestions and revision.

Funding

No specific grant was received from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Doares SH, Syrovets T, Weiler EW, Ryan CA. Oligogalacturonides and chitosan activate plant defensive genes through the octadecanoid pathway. Proc Natl Acad Sci USA 1995; 92:4095-8; PMID:11607534; http://dx.doi.org/10.1073/pnas.92.10.4095
2. Turner JG, Ellis C, Devoto A. The jasmonate signal pathway. Plant Cell 2002; 14:S153-64; PMID:12045275
3. Van der Does D, Leon-Reyes A, Koornneef A, Van Verk MC, Rodenburg N, Pauwels L, Goossens, A, Körbes, AP, Memelink, J, Ritsema, T. Salicylic acid suppresses jasmonic acid signaling downstream of SCFCOI1-JAZ by targeting GCC promoter motifs via transcription factor ORA59. Plant Cell 2013; 25:744-61; PMID:23435661; http://dx.doi.org/10.1105/tpc.112.108548
4. Zhang L, Xing D. Methyl jasmonate induces production of reactive oxygen species and alterations in mitochondrial dynamics that precede photosynthetic dysfunction and subsequent cell death. Plant Cell Physiol 2008; 49:1092-111; PMID:18535010; http://dx.doi.org/10.1093/pcp/pcn086
5. Fingrut O, Flescher E. Plant stress hormones suppress the proliferation and induce apoptosis in human cancer cells. Leukemia 2002; 16:608-16; PMID:11960340; http://dx.doi.org/10.1038/sj.leu.2402419
6. Kim JH, Lee SY, Oh, SY, Han SI, Park HG, Yoo M, Kang HS. Methyl jasmonate induces apoptosis through induction of Bax/Bcl-XS and activation of caspase-3 via ROS production in A549 cells. Oncol Rep 2004; 12:1233-8; PMID:15547743
7. Rotem R, Heyfets A, Fingrut O, Blickstein D, Shaklai M, Flescher E. Jasmonates: novel anticancer agents acting directly and selectively on human cancer cell mitochondria. Canc Res 2005; 65:1981-993; PMID:15753398; http://dx.doi.org/10.1158/0008-5472.CAN-04-3091
8. Cesari IM, Carvalho E, Figueiredo Rodrigues M, Mendonça BdS, Amôedo ND, Rumjanek FD. Methyl jasmonate: putative mechanisms of action on cancer cells cycle, metabolism, and apoptosis. Int J Biochem Cell Biol 2014; 2014:572097, 25 pages; PMID:24648844; http://dx.doi.org/10.1155/2014/572097.
9. Flescher E. Jasmonates in cancer therapy. Canc Letts 2007; 245:1-10; PMID:16600475; http://dx.doi.org/10.1016/j.canlet.2006.03.001
10. Goldin N, Arzoine L, Heyfets A, Israelson A, Zaslavsky Z, Bravman T, Bronner V, Notcovich A, Shoshan-Barmatz V, Flescher E. Methyl jasmonate binds to and detaches mitochondria-bound hexokinase. Oncogene 2008; 27:4636-43; PMID:18408762; http://dx.doi.org/10.1038/onc.2008.108
11. Arora Ka, Pedersen P. Functional significance of mitochondrial bound hexokinase in tumor cell metabolism. Evidence for preferential phosphorylation of glucose by intramitochondrially generated ATP. J Biol Chem 1988; 263:17422-8; PMID:3182854
12. Chen Z, Zhang H, Lu W, Huang P. Role of mitochondria-associated hexokinase II in cancer cell death induced by 3-bromopyruvate. Biochim Biophys Acta Bioenergetics 2009; 1787:553-60; PMID:19285479; http://dx.doi.org/10.1016/j.bbabio.2009.03.003
13. Asai T, Stone JM, Heard JE, Kovtun Y, Yorgey P, Sheen J, Ausubel FM. Fumonisin B1–induced cell death in Arabidopsis protoplasts requires jasmonate-, ethylene-, and salicylate-dependent signaling pathways. Plant Cell 2000; 12:1823-35; PMID:11041879; http://dx.doi.org/10.1105/tpc.12.10.1823
14. Creelman RA, Mullet JE. Oligosaccharins, brassinolides, and jasmonates: nontraditional regulators of plant growth, development, and gene expression. Plant Cell 1997; 9:1211-23; PMID:9254935; http://dx.doi.org/10.1105/tpc.9.7.1211
15. He Y, Fukushige H, Hildebrand DF, Gan S. Evidence supporting a role of jasmonic acid in Arabidopsis leaf senescence. Plant Physiol 2002; 128:876-84; PMID:11891244; http://dx.doi.org/10.1104/pp.010843
16. Kenton P, Mur LA, Atzorn R, Wasternack C, Draper J. (−)-Jasmonic acid accumulation in tobacco hypersensitive response lesions. Mol Plant Microbe Interact 1999; 12:74-8
17. Mur LA, Kenton P, Atzorn R, Miersch O, Wasternack C. The outcomes of concentration-specific interactions between salicylate and jasmonate signaling include synergy, antagonism, and oxidative stress leading to cell death. Plant Physiol 2006; 140:249-62; PMID:16377744
18. Qu ZL, Zhong NQ, Wang HY, Chen AP, Jian GL, Xia GX. Ectopic expression of the cotton non-symbiotic hemoglobin gene GhHbd1 triggers defense responses and increases disease tolerance in Arabidopsis. Plant Cell Physiol 2006; 47:1058-68; PMID:16854938
19. Repka V. Hydrogen peroxide generated via the octadecanoid pathway is neither necessary nor sufficient for methyl jasmonate-induced hypersensitive cell death in woody plants. Biol Plant 2002; 45:105-15
20. RepkaV, Fischerova I, Šilhárová K. Methyl jasmonate is a potent elicitor of multiple defense responses in grapevine leaves and cell-suspension cultures. Biol Plant 2004; 48:273-83
21. Ueda J, Kato J. Isolation and identification of a senescence-promoting substance from wormwood (*Artemisia absinthium* L.). Plant Physiol 1980; 66:246-9; PMID:16661414
22. Woo HR, Chung KM, Park JH, Oh SA, Ahn T, Hong SH, Jang SK, Nam HG. ORE9, an F-box protein that regulates leaf senescence in Arabidopsis. Plant Cell 2001; 13:1779-90; PMID:11487692
23. Zhang L, Xing D, Wang J, Li L. Rapid and non-invasive detection of plants senescence using a delayed fluorescence technique. Photochem. Photobiol Sci 2007; 6:635-41; PMID:17549265