A New Jasmonic Acid Stereoisomeric Derivative Induces Apoptosis Via Reactive Oxygen Species in Human Melanoma Cancer Cells

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Melanoma is one of the most invasive and deadly forms of skin cancer. Its incidence continues to increase at an alarming rate and contrary to other neoplasms, a relatively younger population is becoming affected by this tumor. Its treatment mainly depends on the time of diagnosis. If realized in the early stage, the surgical excision of this neoplasia is successful; however, its late diagnosis leads to an unfavorable fate. Indeed, in the metastatic stage, melanoma becomes very refractory to conventional therapies and nodal metastasis can be associated with 70% mortality after 10 years (Smalley, 2010). Apoptosis represents an efficient and physiological strategy through which the organism eliminates neoplastic cells; however, melanoma cells, both in vivo and in vitro, are quite refractory to apoptosis. Therefore, the agents that induce apoptotic death of melanoma cancer cells could be useful in controlling this malignancy. In recent years, several studies have evidenced that (-)-jasmonic acid, an important member of the jasmonate family, that is known to accumulate in higher plants and fungi, has anti-cancer activity in vitro and in vivo (Russo et al., 2012). In our recent paper, we showed that a new stereoisomeric derivative of (-)-jasmonic acid, the 3-hydroxy-2(S)-(2Z-butenyl)-cyclopentane-1(S)-acetic acid, obtained by biotransformation with the fungus Gibberella fujikuroi, inducing the apoptotic cell death, selectively inhibited the vitality of human prostate cancer cells more efficiently than (-)-jasmonic acid. Therefore, with the aim of identifying novel agents active against melanoma cancer cells, the present study was undertaken to investigate the effect of this new compound on cell growth and death in human melanoma cell line, A2058. The results show that the tested compound, after 72 h of treatment at 6.25-25 µM concentrations, is cytotoxic for melanoma cells, whereas no significant effects were evident in the nonmalignant fibroblast cells. The morphological changes induced by this tested compound in A2058 cells suggest that it induces cellular alterations typical of cells undergoing apoptosis. The increase of caspase-3 activity observed in melanoma cells confirmed the susceptibility of A2058 to this (-)-jasmonic acid derivative. The hypothesis of apoptosis induction in our experimental conditions was reinforced by a high DNA fragmentation (Comet assay), not correlated to LDH release, a marker of membrane breakdown. To investigate on the mechanisms involved in the evidenced cellular effects, the expression profile of two members of Bcl-2 family, the anti-apoptotic Bcl-2 and the pro-apoptotic Bax was analyzed. It is known that Bcl-2 is actively involved in the development of chemo- and radio-resistance and its upregulation is associated to apoptosis resistance in many tumors, especially melanoma. The decrease of Bcl-2/Bax ratio in A2058 cells is indicative of the involvement of these proteins in the pro-apoptotic effect of the (-)-jasmonic acid derivative on melanoma cell line. Compared to nonmalignant counterparts, cancer cells usually have higher intracellular reactive oxygen species (ROS) levels. These highly reactive molecules regulate cellular proliferation and eventually cooperate to the oncogenic cell transformation. The observed increase of intracellular ROS detected in melanoma cells likely contributes to the tested compound-induced apoptosis. Taken together, the results reported here suggest again that the production of compounds obtained by the biotransformation of (-)-jasmonic acid with G. fujikuroi, may be a source for the synthesis of compounds with more potential antitumor activity, and permit to hypothesize that the combination of 3-hydroxy-2(S)-(2Z-butenyl)-cyclopentane-1(S)-acetic acid with other anti-melanoma cancer therapies could be considered a promising strategy that warrants further in vivo evaluation.