Phytosphingosine can overcome resistance to ionizing radiation in ionizing radiation-resistant cancer cells

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Abstract

Although the majority of cancer cells are killed by inonizing radiation, certain types show resistance to it. We previously reported that phytosphingosine also induces apoptotic cell death in caspase dependent pathway in human cancer cells. In the present study, we examined whether phytosphingosine could overcome radiation resistance in the variant Jurkat clones. We first selected radiation-resistant Jurkat clones and examined cross-responsiveness of the clones between radiation and phytosphingosine. Treatment with phytosphingosine significantly did not affect apoptosis in all the clones, indicating that there seemed to be cross-resistance between radiation and phytosphingosine. Nevertheless, combined treatment of phytosphingosine with radiation synergistically enhanced killing of radiation-resistant cells, compared to radiation or phytosphingosine alone. The pan-caspase inhibitor z-VAD-fmk did not completely inhibit the synergistic cell killing induced by combined treatment of ionizing radiation and phytosphingosine. These results demonstrated that apoptosis induced by combined treatment of radiation and phytosphingosine in radiation-resistant cells was associated with caspase independent pathway. We also found that apoptotic cell death induced by combined treatment of ionizing radiation and phytosphingosine correlated to the increases of ROS. The enhancement of ROS generation induced the loss of mitochondria transmembrane potential. In conclusion, ROS generation in combined treatment of phytosphingosine with radiation significantly induced the translocation of AIF to nucleus from mitochondria, suggesting a potential clinical application of combination treatment of radiation and phytosphingosine to radiation-resistant cancer cells.