ANTITUMOR ACTIVITY OF INGENOL-3-ANGELATE IN HUMAN CERVIX CANCER CELL LINES

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Introduction and objectives: In Brazil, cervix cancer is the third leading cause of cancer death in women. Advanced stages of this neoplasm are currently treated with cisplatin plus radiotherapy. Nevertheless, alternative treatments are necessary to improve the outcome of these patients. The diterpene ester, ingenol-3-angelate (I3A), derived from the plant Euphorbia peplus is a new treatment for actinic keratosis, and has been proposed to induce cell death through protein kinases C modulation. The role of I3A in cancer has been described in leukemia, colon, breast, lung and ovarian cell lines, but its effect in cervix cancer is unknown. We aimed to evaluate the cytotoxicity effect of I3A on 7 cervix cancer cell lines (CCCL). Methods: The in vitro cytotoxicity of I3A was assessed using MTS assay. We also performed western blotting analysis to characterize important proteins related to cell proliferation, cell cycle and DNA damage. Furthermore, the cell death was analyzed by flow cytometry, using the annexin V/propidium iodide (PI) staining. Results and conclusion: I3A exhibited dose-dependent cytotoxic effects on CCCL, with an IC\textsubscript{50} mean ranging from 11.24 to 252.42 µM. The HtTA-1 was the most sensitive CCCL, whereas the SiHa was one of the most resistant CCCL. Flow cytometry further revealed an increase of the number of early apoptotic SiHa cells. However, there was no PARP cleavage on SiHa and HtTA-1 I3A-treated at same time. Furthermore, protein profile analysis showed ERK1/2 upregulation, H2AX activation and p21 expression for both, SiHa and HtTa-1. The PKC isoforms analysis demonstrated activation of PKC pan and especially, in PKD/PKC\mu in Ser\textsuperscript{916} and Ser\textsuperscript{744} residues, an important protein in carcinogenesis. These results showed the antitumor potential of I3A on cervix cancer in vitro, which may induce apoptosis, DNA damage and cell cycle modulation supporting that it may play an important role in cervical cancer treatment.

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