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Meeting abstract

Apoptosis induced by cisplatin but not by 5-FU in colon cancer cells depends on Omi/Htra2 protein

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Background

The most frequent cause of treatment failure in patients with advanced cancer is chemotherapy resistance. One of the mechanisms of chemotherapy resistance is failure to trigger apoptosis of cancer cells. Apoptosis can be induced by two pathways, intrinsic and extrinsic. The intrinsic pathway is activated by mitochondrial release of apoptotic proteins secondary to genomic stress. Omi/Htra2 is one of the released mitochondrial proteins. It is a serine protease which inactivates the family of Inhibitor of Apoptosis Proteins (IAPs).

Materials and methods

In this study, the participation of Omi/Htra2 in cell death induced by the chemotherapeutic agents Cisplatin and 5-Fluorouracil (5-FU) was assessed in human colon cancer cells SW480. 5-FU and Cisplatin induced apoptosis in this cell line as shown by cell morphology and further confirmed by showing cleavage of caspase 3. Both drugs induced apoptosis via the intrinsic pathway as shown by mitochondrial release of cytochorome C.

Results

5-FU and Cisplatin promoted the release of Omi/Htra2 from the mitochondria to the cytosol, as demonstrated by immunofluorescence and western blot assays of subcellular fractions. When cells were exposed to an Omi/Htra2 serine protease inhibitor, UCF-101, cell death was significantly suppressed of cells exposed to Cisplatin, but not to 5-FU. Additionally Omi/Htra2 inhibition partially prevented reproductive cell death measured by clonogenic assays of cells exposed to Cisplatin but not to those exposed to 5-FU

Conclusion

This study shows that Omi/Htra2 participates in cell death induced by CDDP but not by 5-FU in colon cancer cells. In addition, our findings suggest downstream differences in the intrinsic pathway of apoptosis triggered by diverse antineoplastic drugs.