The relationship between cisplatin-induced apoptosis and p53, bcl-2 and bax expression in human lung cancer cells

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Cisplatin is an active anticancer drug for lung cancer, but its effectiveness is restricted by the emergence of resistant cell populations. The recent evidences suggest that the genetic regulation of apoptosis may affect the cellular response to DNA damages by cisplatin. Given the roles of *bcl-2*, *bax* and *p53* in apoptosis, we investigated the effect of their expression on the response to cisplatin to understand the molecular events of cisplatin-resistance in lung cancers. Three parental human lung cancer cell lines and their in vitro selected cisplatin-resistant sublines were examined. Cisplatin-induced cytotoxicity was determined by MTT colorimetric assay. To examine the nature of cell death induced by cisplatin, cells treated with cisplatin were processed for acridine orange and ethidium bromide staining for the detection of the condensed or fragmented chromatin and DNA fragmentation. The endogenous levels of bcl-2, bax and p53 protein expression in lung cancer cells were assessed by Western blot analysis. And to determine the mutation of *p53*, we directly sequenced DNA of polymerase chain reaction-amplified exon 5 to 8 of *p53* gene. Among parental cells, H69 was relatively resistant to cisplatin, which showed delayed and reduced apoptosis. It had *p53* mutation and decreased expression of *p53* and bax. Bcl-2 protein was detectable in this cell line. Although apoptosis was markedly reduced in cisplatin-resistant sublines compared to prarental cells, there was no significant difference in the expression of p53, bcl-2, and bax.

Cisplatin-resistance was associated with the reduced cellular susceptibility to apoptosis. Cancer cells with the natural expression of bcl-2 and *p53* mutation may be more resistant to cisplatin and less susceptible to apoptosis. This suggests that *p53* mutation and *bcl-2* may contribute to the intrinsic resistance to cisplatin in lung cancer. However, further analysis of the functional activity of *p53* and other death-antagonist of *bcl-2* family heterodimerizing with *bax* are needed to understand the acquired cisplatin-resistance in lung cancer.