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Presentation Title: **Hydrogen peroxide mediates the apoptotic effect of cisplatin by downregulating bcl-2 through ubiquitin-proteasomal degradation**

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Poster Board Number: 16

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Susceptibility to apoptosis is an essential prerequisite for successful eradication of tumor cells by chemotherapy. Consequently, resistance to apoptosis has been established as one of the mechanisms responsible for the failure of therapeutic approaches in many types of cancers. In the present study, we investigated the susceptibility of human lung epithelial cancer cells to apoptotic cell death induced by cisplatin and determined its regulatory mechanisms. Treatment of the cells with cisplatin induced rapid generation of reactive oxygen species (ROS) and a concomitant increase in apoptotic cell death. Death induced by cisplatin was found to be mediated through the mitochondrial pathway which requires caspase-9 activation and is dependent on Bcl-2 expression. Inhibition of caspase activity by caspase-9 inhibitor (z-LEHD-fmk) or by overexpression of Bcl-2 potently inhibited apoptosis induced by cisplatin. Bcl-2 was downregulated by cisplatin treatment through ubiquitin-proteasomal degradation which was mediated by ROS. Inhibition of ROS by the antioxidant enzyme catalase or glutathione peroxidase (H_2O_2 scavenger), but not by superoxide dismutase ($O_2^{\bullet -}$ scavenger) or sodium formate ($OH^{\bullet}$ scavenger), inhibited cisplatin-induced Bcl-2 downregulation. Bcl-2 dephosphorylation which controls its stability was also induced by cisplatin and was inhibited by catalase. Together, our results indicate an essential role of H_2O_2 in the regulation of Bcl-2 stability and apoptotic cell death induced by cisplatin. Since Bcl-2 is overexpressed in many cancer cell types and resistance to cisplatin-induced apoptosis is a major limitation for effective therapy, the knowledge from this study could be beneficial to the design of more effective therapy for cancer treatment.

Key words: cancer, regulation, peroxide, lung, therapeutic agents

The findings and conclusions in this abstract have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent agency determination or policy.

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