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UNDERSTANDING CISPLATIN DRUG RESISTANCE IN HUMAN OVARIAN CANCER

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ABSTRACT

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This dissertation describes a scientific approach in understanding the mechanism of cisplatin drug resistance in human ovarian cancer. Ovarian cancer is the fifth leading cause of death from all cancers in women. Platinum-based chemotherapeutic drugs are the primary treatment for ovarian cancer. Most patients with the disease are initially responsive to chemotherapeutic treatment. However, the majority of ovarian cancer patients eventually relapses and becomes refractory to additional treatment. This drug resistance becomes a major impediment to the successful treatment of ovarian cancer. To date the mechanism of drug resistance is still poorly understood. To elucidate the underlying mechanisms in which drug resistance is developed in ovarian cancer, global protein expression profiling in drug-sensitive and -resistant ovarian cancer cells need to be established.

Cisplatin is believed to kill cancer cells by crosslinking to DNA and interfering with its replication/repair mechanism, eventually leading to cell death. Many ovarian cancer cells become resistant to cisplatin through overexpression or mutation of one or more proteins involved in the drug's target. The objective of this study is to understand the mechanism by which cisplatin drug resistance arises in ovarian cancer using proteomics technologies. It is our hypothesis that cisplatin resistance is a multifactorial event and involves changes in the expression of various protein factors contributing to cytoprotection against cisplatin, thus modulation of these proteins will enable us to sensitize cisplatin resistance in ovarian cancer cells. Through the use of proteomics technologies and bioinformatics, we identified that Superoxide dismutase 1 (SOD1) is a major player involved in cisplatin resistance. Validation of its overexpression in cisplatin-resistant cells and modulation of its activity showed that SOD1 is a key determinant of cisplatin resistance in ovarian cancer. This study not only demonstrates the power of state-of-the-art technologies, but also provides valuable information about potential biomarker(s) for diagnostics and drug candidate(s) to overcome drug resistance.

Mu Wang, Ph.D., chair

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