Yeast as a model system to study mechanisms regulating cisplatin sensitivity and resistance

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Cisplatin is a highly effective chemotherapeutic drug used in the treatment of several tumors. It is a DNA-damaging agent that induces apoptosis of rapidly proliferating cells, an important factor underlying its therapeutic efficacy. Unfortunately, cellular resistance occurs often. A large fraction of tumor cells harbor mutations in p53, contributing to defects in apoptotic pathways and drug resistance. However, cisplatin-induced apoptosis can also occur in p53 deficient cells; thus, elucidation of the molecular mechanism involved will potentially yield new strategies to eliminate tumors that have defects in the p53 pathway.

Most of the studies in this field have been conducted in cultured mammalian cells, not amenable to systematic genetic manipulation. Therefore, we aimed to establish a simplified model to study cisplatin-induced apoptosis using the yeast *Saccharomyces cerevisiae.* Our results indicate cisplatin induces an active form of cell death in yeast, as this process was partially dependent on new protein synthesis and did not lead to loss of membrane integrity. Preliminary studies of apoptotic markers revealed mitochondrial fragmentation and chromatin condensation after cisplatin exposure. Deletion of Yca1p, the yeast metacaspase, did not protect cells from cisplatin-induced cell death, although exposure of yeast cells to cisplatin resulted in an increase in proteolytic activity that was inhibited *in vitro* by MG132, a commonly used proteasome inhibitor. *In vivo*, co-incubation with MG132 increased resistance to cisplatin and, accordingly, yeast strains deficient in proteasome proteolytic activity were more resistant to cisplatin than wild type strains. Proteasome inhibitors induce apoptosis in various cell types, whereas in others they prevent apoptosis induced by different stimuli. Our results indicate inhibition of the proteasome protects from cisplatin-induced apoptosis in budding yeast. The molecular mechanism involved is under characterization.

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