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# Identification of evolutionarily conserved DNA damage response genes that alter sensitivity to cisplatin

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## Abstract

Ovarian, head and neck, and other cancers are commonly treated with cisplatin and other DNA damaging cytotoxic agents. Altered DNA damage response (DDR) contributes to resistance of these tumors to chemotherapies, some targeted therapies, and radiation. DDR involves multiple protein complexes and signaling pathways, some of which are evolutionarily ancient and involve protein orthologs conserved from yeast to humans. To identify new regulators of cisplatin-resistance in human tumors, we integrated high throughput and curated datasets describing yeast genes that regulate sensitivity to cisplatin and/or ionizing radiation. Next, we clustered highly validated genes based on chemogenomic profiling, and then mapped orthologs of these genes in expanded genomic networks for multiple metazoans, including humans. This approach identified an enriched candidate set of genes involved in the regulation of resistance to radiation and/or cisplatin in humans. Direct functional assessment of selected candidate genes using RNA interference confirmed their activity in influencing cisplatin resistance, degree of γH2AX focus formation and ATR phosphorylation, in ovarian and head and neck cancer cell lines, suggesting impaired DDR signaling as the driving mechanism. This work enlarges the set of genes that may contribute to chemotherapy resistance and provides a new contextual resource for interpreting next generation sequencing (NGS) genomic profiling of tumors.

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## Keywords

DNA damage response, Head and neck cancer, Platinating agents, Resistance

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