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translational research

1557P Identification of evolutionarily conserved DNA damage response (DDR) genes that alter sensitivity to cisplatin

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Background: Cisplatin is one of the most potent chemotherapeutic agents currently in use for clinical treatment of many types of cancer, including head and neck cancers (HNCs) and epithelial ovarian cancers (EOCs). Like other platinum agents, it is thought to function primarily by modifying DNA, forming intrastrand crosslinks and other DNA lesions. The molecular mechanisms of resistance to cisplatin are not fully understood, although some forms of resistance have been associated with changes in DNA Damage Response (DDR). Identification of the new therapeutic targets would both allow a better understanding of drug resistance mechanisms, and potentially provide new avenues for disease management.

Methods: We have integrated data from a large number of functional screens performed in lower eukaryotes for genes conferring resistance to cisplatin and other DNA damaging agents such as g-ray-, X-ray-, and UV-radiation. We subsequently identified human orthologues of evolutionary conserved genes that are potentially involved in DDR and cisplatin sensitivity in humans. We then directly tested the role of some of these genes in response to the exposure to the DNA damaging agents in EOC and HNC cell lines. We used small interfering RNAs (siRNAs) to deplete either control genes or candidate genes of interest, and under basal and drug-treatment conditions, we assessed cell viability,the impact on phospho-H2AX focus formation, and activation of the ATR DDR kinase. Besides cisplatin, we assessed gene effect on two additional DNA damaging drugs, 5-fluorouracil and olaparib.

Results: We identified in silico a set of candidate human genes with yeast orthologs that are implicated in DDR and regulation of cisplatin sensitivity in Saccharomyces cerevisiae, developing a novel genomic resource. Depletion of a set of empirically tested genes sensitized human cancer cells to cisplatin and other DNA damaging drugs, and affected phospho-H2AX foci and DDR signaling.

Conclusions: Our findings suggest that possible mechanism of sensitization to cisplatin caused by depletion of these genes involves reduced activation of DDR responses, and identifies new, non-canonical candidate regulators of DDR based on evolutionary analysis.

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