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Platinum Resistance: The Role of DNA Repair Pathways

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Platinum chemotherapeutic agents such as carboplatin, cisplatin and oxaliplatin are used to treat a broad range of malignant diseases. Unfortunately, their efficacy in most cancers is limited by the development of resistance. Multiple factors contribute to platinum resistance but alterations of DNA repair processes have been known for some time to be important in mediating resistance. Cisplatin and carboplatin work by binding to DNA and forming DNA adducts leading to cross-links which disrupt the structure of the DNA molecule, leading to steric changes in the helix. This alteration in the structure of the DNA molecule leads to cellular DNA damage recognition and repair which can result in the continued viability of the cell resulting in platinum resistance.

There are five recognized DNA pathways that protect cellular DNA from injury: nucleotide excision repair (NER), mismatch repair (MMR), double strand break repair, base excision repair and direct repair. But this write up will focus on two most important mechanisms known to be involved in platinum response i.e. NER and MMR. Also, the therapeutic implications of alterations in DNA repair which affect response to platinum such as excision repair cross-complementation group 1 (ERCC1) deficiency and mismatch repair deficiency is reviewed. Further, their importance in patient prognosis in the clinical setting is assessed.

Nucleotide Excision Repair functions by a "cut and-paste" mechanism in which cisplatin damage recognition, local opening of the DNA helix around the lesion, damage excision, and gap filling occur in successive steps. The ERCC1 protein plays a fundamental role in nucleotide excision repair. Small retrospective clinical trials of ovarian, colorectal, and non-small cell lung cancer have shown an inverse correlation of ERCC1 mRNA levels with either response to platinum therapy or survival. More recently, the International Adjuvant Lung Cancer trial retrospectively evaluated ERCC1 protein expression and reported a statistically significant survival benefit in patients with low levels of ERCC1 who had received platinum-based chemotherapy compared to patients with low levels of ERCC1 who did not receive chemotherapy and patients with high levels of ERCC1 who received cisplatin chemotherapy. Further, completely resected NSCLC patients with ERCC1 negative tumors benefitted from cisplatin-based chemotherapy but those with ERCC1 positive tumors did not. Results of the first prospective randomized trial using ERCC1 mRNA levels to assign chemotherapy in patients with NSCLC revealed that patients in the experimental arm (genotypically assigned in which patients with high levels of ERCC1 received non-platinum containing regimen of gemcitabine/docetaxel and patients with low ERCC1 expression received cisplatin/docetaxel) had a statistically significant improvement in response rate compared with the patients of the control arm (docetaxel/ cisplatin).

The Mismatch Repair Pathway. A functional MMR system is required for the detection of damaged DNA created by cisplatin and carboplatin. Platinum complexes interfere with normal MMR activity and prevent a repair from being completed. Inability to complete the repair of the DNA damage leads to apoptosis. When MMR is deficient, cells can continue to proliferate in spite of DNA damage caused by platinating agents, and are thus resistant. The *MLH1* and *MSH2* (Mut S homologue 2) genes seem to be particularly important in the normal function of the MMR system. MMR deficiency seems to confer resistance to cisplatin and carboplatin, and not to oxaliplatin. MMR proteins do not recognize adducts formed by oxaliplatin, and the repair pathway is not triggered. Thus, oxaliplatin has activity in cells that are resistant to cisplatin and carboplatin. Results of retrospective analysis in patients with advanced NSCLC treated with gemcitabine and oxaliplatin versus gemcitabine and cisplatin revealed a statistically significant difference in the response rate in patients with hMSH2 deficiency (38% gemcitabine/oxaliplatin versus 0% gemcitabine/cisplatin), suggesting that oxaliplatin is active in cells with MMR deficiency. Additionally, it has been shown that the loss of either p53 or MMR function resulted in platinum resistance but resistance occurred more rapidly in cells defective in both p53 and MMR.

In conclusion, evaluation of DNA repair pathways at molecular level, expands the likelihood to predict response to treatment and ultimately may lead to more individualized, targeted and more effective therapies.