Published in final edited form as:
Cancer Discov. 2014 October ; 4(10): 1118–1119. doi:10.1158/2159-8290.CD-14-0893.

Testing the metal of ERCC2 in predicting the response to platinum-based therapy

John J. Turchi[1,2,*], **Derek S. Woods**[2,^,#], and **Pamela VanderVere Carozza**[1,#]

[1]Department of Medicine

[2]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, 980 W Walnut St, Joseph E Walther Hall R3-C562, Indianapolis IN, 46202

Summary

The role of DNA repair has been shown to impact the cellular response to platinum-based therapy in a variety of cancers, however, translating this knowledge to the clinic has proven difficult and yielded mixed results. In this issue of *Cancer Discovery*, Rosenberg, Garraway and colleagues have analyzed responders and non-responders to neo-adjuvant platinum-based therapy with locally advanced urothelial cancer and identified a series of mutations in the nucleotide excision repair (NER) gene *ERCC2* that correlate with the response to platinum-based therapy (1). This work provides evidence that defects in nucleotide excision repair can be exploited to maximize the efficacy of conventional platinum-based chemotherapy.

It has been estimated that 750,000 patients per year will receive a platinum-based chemotherapeutic in the treatment of their cancer. While curative in a small sub-set of cancers, most tumors show a mixed response. The ability to predict which patients will respond and those that will not has been the subject of intense study in many cancers with mixed results. Platinum-based agents impart their clinical efficacy via the formation of direct Pt-DNA adducts and thus DNA repair pathways have been intensively studied. One of the most studied associations with platinum sensitivity is the expression of ERCC1, a component of the NER nuclease that cleaves DNA 5' of the cisplatin DNA adduct. These studies have been hampered by inconsistent and non-specific reagents in analysis of expression via immunohistochemistry (2) and variant isoforms complicating gene expression as measured by mRNA (3). While hints of interesting associations have been uncovered in a variety of cancers, large scale validation of ERCC1 as a target remains. Similarly, the extreme sensitivity of germ cell tumors to cisplatin was initially correlated with reduced NER protein expression (4). More recently, other determinants of sensitivity have been suggested that contribute the clinical efficacy of cisplatin in germ cell tumors (5).

The analysis of NER genes and expression has also been extended to carcinogenesis as most cancers are thought to harbor defects in some aspect of DNA repair that contributes to

[*]Corresponding author.
[#]Contributed equally
[^]Current address NERx Biosciences, 351 W. 10 St, Suite 510, Indianapolis IN 46202

No potential conflicts of interest were disclosed by the authors.

genome instability (6). Expression analysis of DNA repair genes in both carcinogenesis and response to therapy has been disappointing. This however, is not surprising, as the initiation of most DNA repair pathways in humans are not regulated by transcriptional mechanisms. This makes some degree of sense in that transcription is often inhibited by the DNA damage itself and therefore the low but constitutive expression of repair proteins is required to allow cells to respond to the damage without requiring regulation via DNA repair gene expression. This may not be immediately obvious as the transcription factor p53 is often grouped with DNA repair factors such as those involved in the direct repair of Pt-DNA adducts. This classification however is somewhat tangential in that p53 is not required for the direct repair of damage and is instead involved in the DNA damage response signaling cascades (7). Thus regulation of these direct DNA repair pathways is more influenced by localization, protein signaling cascades, and protein-protein interactions than by mRNA levels. The analysis of single nucleotide polymorphisms has also yielded disparate results. While a numerous correlations have been established, few if any have been validated and progressed to clinical utility. Recent meta-analysis of 23 studies and over 15,000 patients suggests certain *ERCC2* SNPs correlate with increased risk of bladder cancer (8), but no correlation with response to therapy.

Whole exome sequencing, the approach taken in the study by Garraway and Rosenberg (1) offers some advantages, but continues to rely on the subjective assessment of existing knowledge for the selection of candidate genes to be analyzed in detail. This is evidenced by the fact that *ERCC2* was not identified as a statistically significantly mutated gene in the cohort-wide analysis. Previous work that demonstrated that *ERCC2* is often mutated in bladder cancer (9) and the role of XPD in NER (10) provided the impetus to further investigate *ERCC2* and resulted in the demonstration that *ERCC2* was the only gene significantly enriched in the responder cohort, with all *ERCC2* non-synonymous somatic mutations occurring in the cisplatin-sensitive tumors (1).

The demonstration that the clinically identified mutations fail to correct an XPD-null cell line provides strong evidence that the inhibition of DNA repair is what is resulting in the sensitivity to cisplatin. The clustering of the mutants in the helicase domains also strengthens that argument. However, the mechanism by which *ERCC2* mutations correlate with complete pathologic response to cisplatin in muscle-invasive urothelial cancer may be more complex as each of the mutations was identified in only one of the *ERCC2* genes. Therefore the tumors harbored *ERCC2* mutations in the presence of a wild-type allele of *ERCC2*. This raises the interesting question of whether forced expression of one of the clinically identified *ERCC2* mutants in a wt-*ERCC2* bladder cancer cell line would still result in sensitivity to cisplatin and implicate a dominant negative effect? The alternative is that increased sensitivity to cisplatin is a function of expression via haplo-insufficiency; however, there is no evidence to suggest that XPD expression is limiting NER activity.

The exome sequence data also brings out an interesting point with regard to mutation load. Interestingly, the tumors harboring *ERCC2* mutations had a 3-fold increase in mutational burden per megabase compared to the tumor harboring wild type-*ERCC2*. This suggests that the mutation in the *ERCC2* gene may have occurred early in the carcinogenesis process and the decreased repair capacity resulted in the accumulation of mutations. If *ERCC2* mutation

is an early event, the potential for tumor heterogeneity resulting in obtaining a biopsy of an *ERCC2* wild type section of the tumor is less likely. Also, the complete pathological response observed is consistent with the entire tumor being *ERCC2* mutant. This bodes well for the potential that the diagnostic test could be employed to identify the patients most likely to benefit from Pt-based neo-adjuvant chemotherapy. The challenge ahead will be to confirm the utility of *ERCC2* mutation analysis in urothelial cancer in prospective trials. A broader impact of this work is also possible. While *ERCC2* mutations are lower in other cancers, the potential exists that these would also be hyper sensitive to Platinum-based therapy. Similarly there are 32 gene products that participate in the NER pathway and mutation in many of these would be predicted to have similar impacts on platinum sensitivity. The finding that the only NER gene significantly mutated in the bladder cancer responders is *ERCC2* suggest a more complex interaction may be in play between the NER proteins in any given cancer type.

Acknowledgments

Supported by NIH grant R01 CA180710 to JJT

Reference List

(1). Garraway LA, Rosenberg JE. Cancer Discov. 2014

(2). Besse B, Olaussen KA, Soria JC. ERCC1 and RRM1: ready for prime time? J Clin Oncol. 2013; 31:1050–60. [PubMed: 23401439]

(3). Friboulet L, Olaussen KA, Pignon JP, Shepherd FA, Tsao MS, Graziano S, et al. ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. N Engl J Med. 2013; 368:1101–10. [PubMed: 23514287]

(4). Welsh C, Day R, McGurk C, Masters JRW, Wood RD, Koberle B. Reduced levels of XPA, ERCC1 and XPF DNA repair proteins in testis tumor cell lines. Int J Cancer. 2004; 110:352–61. [PubMed: 15095299]

(5). Koberle B, Roginskaya V, Zima KS, Masters JR, Wood RD. Elevation of XPA protein level in testis tumor cells without increasing resistance to cisplatin or UV radiation. Mol Carcinog. 2008; 47:580–6. [PubMed: 18240296]

(6). Alberts B. Redefining cancer research. Science. 2009; 325:1319. [PubMed: 19745119]

(7). Cavallo F, Feldman DR, Barchi M. Revisiting DNA damage repair, p53-mediated apoptosis and cisplatin sensitivity in germ cell tumors 1. Int J Dev Biol. 2013; 57:273–80. [PubMed: 23784838]

(8). Li X, Xu J, Yang X, Wu Y, Cheng B, Chen D, et al. Association of single nucleotide polymorphisms of nucleotide excision repair genes with laryngeal cancer risk and interaction with cigarette smoking and alcohol drinking. Tumour Biol. 2014; 35:4659–65. [PubMed: 24563277]

(9). Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014; 507:315–22. [PubMed: 24476821]

(10). Marteijn JA, Lans H, Vermeulen W, Hoeijmakers JH. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 2014; 15:465–81. [PubMed: 24954209]