It has been estimated that 750,000 patients per year will receive a platinum (Pt)-based chemotherapy in the treatment of their cancer. Although Pt-based chemotherapy is curative in a small subset of cancers, most tumors show a mixed response. The ability to predict which patients will respond and which will not has been the subject of intense study in many cancers, with mixed results. Pt-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 Pt sensitivity is the expression of ERCC1, a component of the nucleotide excision repair (NER) nuclease that cleaves DNA 5′ of the cisplatin DNA adduct. These studies have been hampered by inconsistent and nonspecific reagents in analysis of expression via immunohistochemistry (1) and variant isoforms complicating gene expression as measured by mRNA (2). Although hints of interesting associations have been uncovered in a variety of cancers, the 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 (3). More recently, other determinants of sensitivity have been suggested that contribute to the clinical efficacy of cisplatin in germ cell tumors (4).

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 genome instability (5). 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 is 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 (6). Thus, regulation of these direct DNA repair pathways is influenced more by localization, protein signaling cascades, and protein–protein interactions than by mRNA levels. The analysis of SNPs has also yielded disparate results. Although numerous correlations have been established, few, if any, have been validated and progressed to clinical utility. Recent meta-analysis of 23 studies and more than 15,000 patients suggests that certain ERCC2 SNPs correlate with increased risk of bladder cancer (7), but no correlation was found with response to therapy.

Whole-exome sequencing, the approach taken in the study by Van Allen and colleagues in this issue (8), 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 nonsynonymous somatic mutations occurring in the cisplatin-sensitive tumors (8). 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 results 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 alleles. Therefore, the tumors harbored ERCC2 mutations in the presence of a wild-type (WT) 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 haploinsufficiency; however, there is no evidence to suggest that XPD expression is limiting NER activity.

The exome sequence data also bring 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 with the tumors harboring WT-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 WT section of the tumor is less likely. Also, the complete pathologic response observed is consistent with the entire tumor being ERCC2 mutant. This bodes well for the potential that the diagnostic test could be used to identify the patients most likely to benefit from Pt-based neoadjuvant 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. Although ERCC2 mutations are lower in other cancers, the potential exists that these would also be hypersensitive to Pt-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 Pt sensitivity. The finding that the only NER gene significantly mutated in the bladder cancer responders is ERCC2 suggests that a more complex interaction may be in play between the NER proteins in any given cancer type.

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