Praz and colleagues report in this issue on the relationship between the occurrence of a polymorphism of ERCC1 in tumor tissues of patients with colorectal cancer and the rate of disease response to the combination of oxaliplatin and 5-fluorouracil (1). This polymorphism is associated with reduced translation of the gene, and presumably, reduced DNA repair capability. Their report suggests that the ability of cells/tissues to up-regulate ERCC1 seems to be correlated with whether or not the patient will respond to oxaliplatin-based therapy. This ERCC1 polymorphism, and its implications, was first reported by others (2, 3). It is important to understand the molecular pharmacology of oxaliplatin, as well as the basic issues about ERCC1.

Oxaliplatin is the third platinum analogue to be approved by the Food and Drug Administration for clinical use. Cisplatin, carboplatin, and oxaliplatin have a number of molecular differences, but are similar in critical ways (4). The most important similarities revolve around the cis configuration of the two reactive groups of the platinum core of the molecule. This cis bond angle is relatively fixed and results in covalent bonding with DNA and other molecules, where the target molecule conforms to fit the bond angle of the platinum moiety. In the case of platinum-DNA adduct, this fixed bond angle for platinum results in bifunctional DNA lesions that contort the DNA to accommodate the platinum. Thus, DNA kinking is a major feature of platinum-DNA damage, which is recognized and repaired by the nucleotide excision repair pathway. Structurally, similar lesions are formed with DNA after interactions with UV light and with polycyclic aromatic hydrocarbons, all of which are recognized and repaired by nucleotide excision repair.

There are four basic DNA repair pathways: nucleotide excision repair, base excision repair, mismatch repair, and double-strand break repair (5–7). Each pathway has its own set of proteins that function entirely independently of the other pathways. Experimental data suggest that there is also cross-functionality of these pathways, but for the most part, these four pathways are separate. Nucleotide excision repair processes bulky lesions such as UV dimers, 6-4 UV photoproducts, polycyclic aromatic hydrocarbons, and cisplatin-DNA lesions. Base excision repair processes oxidative DNA damage and simple alkylation damage to DNA bases. Mismatch repair processes DNA strand slippage, mismatches in DNA base alignments, and ensures fidelity of replication during cellular division. Double-strand break repair is critically important for protecting against particularly potent DNA damaging agents, such as X-ray irradiation.

ERCC1 is an excision nuclease within the nucleotide excision repair pathway (5–7). ERCC1 forms a heterodimer with XPF. As a unit, they execute the 5'-incision into the DNA strand, relative to the site of DNA damage, in the nucleotide excision repair excision process. Studies by Sancar and Reardon (6) show that the 5' excision is the last of several steps that are specific to excision of a platinum-DNA lesion. ERCC1 is one of the 16 proteins that compose the nucleotide excision repair reairosome.

ERCC1 is highly conserved through nature, with analogues in E. coli and in plants (5, 7–9). The gene is located on chromosome 19 and has 10 exons spread over ~15 kb of genome. Multiple splice variants of the full-length gene product have been described or hypothesized to exist. A functional ERCC1 is essential to life. Mice with an ERCC1 knockout die shortly after weaning, and there is one case in the literature of a human baby that died shortly after birth who may have had a nonfunctional ERCC1. In mouse models, normal ERCC1 function is critical to normal aging, normal brain development, and normal immunoglobulin switching. The only cell line that exists without a functional ERCC1 is very difficult to maintain in culture. Therefore, we have comparatively little direct knowledge about ERCC1 functionality. This gene may be important in several biological pathways that are not yet fully described.

Based on studies done in the laboratory, we understand some of the issues that relate to the ERCC1 influence on repair of platinum-DNA damage. In Chinese hamster ovary cells that have a defective ERCC1, transfection of ERCC1 into those cells restores the ability to repair cisplatin-DNA adduct (10). Human ovarian cancer cells that express ERCC1 mRNA to higher levels also show higher levels of resistance to platinum drug exposures (11). Where ERCC1 is up-regulated, so are the other genes in the nucleotide excision repair reairosome (12). The presence of alternatively spliced ERCC1 mRNA is inversely related to DNA repair efficiency in a range of cell lines (13–15). Up-regulation of ERCC1, XPA, and other nucleotide excision repair genes occurs in the absence of mutations or gene amplifications of these genes (16, 17). Transfection of a dominant negative to activator protein 1 into human ovarian cancer cells down-regulates ERCC1 and sensitizes cells to cisplatin (18). In addition, drugs that down-regulate ERCC1 also inhibit cisplatin-DNA adduct repair and make the treated cells more sensitive to platinum drugs (reviewed in ref. 3). ERCC1 has several splice variants and one known polymorphism that seems to influence the...
activity of the full-length gene product (2, 3, 13–15). This polymorphism seems to reduce the rate at which translation of the gene into protein can occur.

The regulatory control of ERCC1 expression is also of substantial interest. ERCC1 appears to be up-regulated by activator protein 1, which in this case is a heterodimer of jun and fos (19). This up-regulation can be effected through the jun kinase system or the extracellular signal-regulated kinase system. The bigger picture, however, is more interesting. ERCC1 is one of the 16 proteins in the nucleotide excision repair repairosome. A computer-based analysis was done to assess the possibility that all 16 of these proteins might be regulated by the same transcription factors (20). The analysis strongly suggests this possibility. Further, in each case where it has been studied, the genes in the nucleotide excision repair repairosome (ERCC1, XPA, XPB, XPD, etc.) are highly expressed together or expressed in low levels together (refs. 11, 21–25, and other reports). Activator protein 1 is clearly an important positive transcriptional regulator, and there are several candidates for clinically important negative transcriptional regulators. A more detailed study of the in vitro effects of specific transcription factors on each of the nucleotide excision repair repairosome proteins has yet to be done.

One practical aspect of these 16 nucleotide excision repair genes being acted on by the same regulatory proteins has to do with overall DNA repair function. Known DNA repair defects are the result of one specific protein being mutated or not present. Conversely, it is clear that for the DNA repair system to work best, all proteins in this process should be up-regulated together, down-regulated together, etc. This has been studied in human brain tissues as well as in cell lines. In brain tissues (24, 25), normal tissues have tightly coordinated mRNA expressions of all studied genes within the nucleotide excision repair repairosome. This suggests excellent DNA repair efficiency. High-grade malignant brain tissues have a much reduced level of coordination of mRNA expression patterns for the same genes. This suggests much lowered DNA repair efficiency. Low-grade malignant brain tissues have a pattern that is intermediate between the two. This has been interpreted to offer one reason why malignant brain tissues will show greater sensitivity to DNA damaging agents than the adjacent normal brain tissues when they are concurrently exposed. Thus, one has a differential in tissue sensitivity to DNA damaging therapies related to DNA repair efficiency.

One study attempted to assess whether or not there was an up-regulation of these genes, or if these genes were independently regulated. The study assessed the static representation of several nucleotide excision repair genes from the repairosome in human ovarian cancer tissues (26). The study suggested that ERCC1 up-regulation must occur first in the nucleotide excision repair cascade (26). However, even if the suggested order of genes is not mandatory, the polymorphism reported (1–3) would result in limited available ERCC1 protein, which would limit the activity of the nucleotide excision repair process.

Malignancies in which mRNA expression of ERCC1 is directly related to clinical outcome in response to DNA damaging chemotherapy include lung cancer, head and neck cancers, gastric cancer, colorectal cancer, and ovarian cancer (data reviewed in ref. 3). Tissue culture studies suggest that other diseases where this relationship might be important include testicular cancer, bladder cancer, cervical cancer, and others (data reviewed in ref. 3). This leaves open the question on why ERCC1 protein does not show similar correlations. It is the view of this author that ERCC1 protein that is active is complexed with the 15 other proteins in the nucleotide excision repair repairosome, and is not readily accessible to antibody binding. This would explain the difficulty in assessing the active portion of total ERCC1 protein (i.e., that which is truly participating in the DNA repair process). Meanwhile, mRNA levels of ERCC1 have repeatedly shown to be useful in giving clinically relevant information about the nucleotide excision repair pathway.

The current study (1) indicates that molecular assessment of the tumor tissues may give meaningful clinical information with respect to planning platinum-based therapies. This study also provides evidence to suggest the possibility that we may learn to pharmacologically exploit our emerging knowledge of nucleotide excision repair (and possibly other DNA repair pathways) for clinical benefit.

References


ERCC1 and Clinical Resistance to Platinum-Based Therapy
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