It has been estimated that there is a 90% overlap between mutagenicity and carcinogenicity of environmental chemicals (1) and that environmental exposure to carcinogens contributes to the development of more than 80% of human cancers (2). Cancer is also considered to be a genetic disease because genetic alterations at either chromosomal or gene levels have been identified in most cancers. In multistep carcinogenesis (3), initial damage to DNA may lead to tumorigenesis and/or carcinogenesis due to functional imbalance between oncogenes (4), tumor suppressor genes (5), and DNA repair genes (6), perhaps as a result of mutation fixation of the damage. During carcinogenesis, both endogenous and exogenous exposures to carcinogens or genotoxic agents cause cell cycle delays (7) that allow cells to repair DNA damage, suggesting that efficient DNA repair is central to maintaining normal cell cycle and growth.

Evidence from molecular epidemiology supports the notion that DNA repair capacity is one of the determinants of genetic susceptibility to cancer (8). Individuals with defective DNA repair genes have up to 1000-fold increased risk for developing cancer. This is exemplified by the presence of defective nucleotide excision repair genes in xeroderma pigmentosum (9), defective mismatch repair genes in patients with hereditary non-polyposis colon cancer (10), and defective BRCA1 and BRCA2 genes in breast cancer (11). This etiologic association between deficient DNA repair and increased cancer risk is also supported by evidence from studies of sporadic cancers of the skin (12), lung (13), colon (14), and breast (11). These data strongly suggest that it is important for normal tissues to have efficient DNA repair so as to eradicate DNA lesions caused by carcinogens, thereby reducing the risk of mutation fixation and subsequent development of cancer.

Clues are beginning to emerge with regard to the mechanism by which defects in hMSH6, hMSH2, and hMLH1 genes can give rise to resistance to chemotherapeutic agents. In humans, an hMSH2/hMSH6 heterodimer (MutSα) recognizes mismatches of DNA as well as insertion and deletion loops (15–17). It can also recognize damaged DNA base pairs containing O6-methylguanine, O4-methylthymine, or the cisplatin–d(GpG) adduct (18). hMSH2 also forms a heterodimer with hMSH3, and this complex (MutSβ) mediates the repair of insertion and deletion loops (15–17). hMLH1 forms heterodimers with hPMS1, hPMS2, and hMLH3; however, at the present time, hMLH1/hPMS2 (MutLo) is the only heterodimer for which there is evidence for participation in the mismatch repair function. The hMutLo protein forms a complex with hMutSa or hMutSβ, and the repair complex directs the DNA repair process (16,17,19).

Normally, the hMutLo–hMutSa complex triggers G2–M arrest followed by an apoptotic response in normal cells (20). It is thought that this is due, at least in part, to signaling by the complex that represents the first step in a damage-signaling cas-
cade. Not all of the molecular events in this cascade have been elucidated, but it is known that, as a part of this cascade, p53 is phosphorylated at Ser-15 and Ser-392 (21). This selective phosphorylation of p53 after certain kinds of DNA damage may be part of the signal from p53 of the damaged DNA response, resulting in the activation of p53 and an arrest of cell cycle progression. Cells with a defective hMutLo/hMutSβ complex fail to elicit this G1 checkpoint response when they are treated with these agents. The cells are, therefore, tolerant of DNA lesions that are otherwise lethal to mismatch repair-proficient cells.

In the clinical setting, many therapeutic agents, such as platinum drugs, nitrogen mustards, chloroethylnitrosoureas, and radiotherapy, induce DNA damage and cause cell killing (22). However, any enhanced DNA repair, such as nucleotide excision repair for bifunctional DNA adducts induced by platinum-based chemotherapy (23) and O6-alkylguanine DNA alkyltransferase for O6-guanine induced by alkylating agents (24), will effectively reduce the anticancer effect of these agents. Under such circumstances, tumors with enhanced nucleotide excision repair have an intrinsic resistance to radiotherapy and chemotherapy (25), leading to continued growth and metastasis (26). Nevertheless, tumors defective in mismatch repair have resistance to DNA-methylating agents, 5-fluorouracil, and radiotherapy through a mechanism of tolerance (27).

In this issue of the Journal, Chen et al. (28) provide us with a new insight into mismatch repair and colon carcinogenesis. They explored the possible etiologic role of environmental exposure to carcinogens and the potential of developing new chemotherapeutic agents by studying two related cell lines, HCT116 and HCT116+C3, with deficient mismatch repair and by correcting mismatch repair by an exogenous chromosome 3. In response to a frameshift mutation inducer, 6-chloro-9-[3-(2-chloroethylamino)propylamino]-2-methoxy-acridine (ICR191), cells with defective mismatch repair had a much higher mutation rate and a poorer survival than cells with corrected mismatch repair.

Chen et al. propose two possible mechanisms for this increased sensitivity to ICR191 in mismatch repair-deficient cells. First, it could be due to the high mutation rate seen in mismatch repair-deficient cells, resulting in an increased number of mutations relative to that seen in the mismatch repair-proficient cells. A second hypothesis is that the mismatch repair pathway as well as a second repair pathway might be involved in the response of mismatch repair-deficient cells. In such a case, the alternate pathway would induce or send signals for the apoptotic response that the defective mismatch repair had failed to elicit. The findings of Chen et al. add to our understanding that colon carcinogenesis in cells with defective mismatch repair occurs after sufficient somatic mutations have been accumulated as a consequence of exposure to mutagens or carcinogens in the gut. In spite of resistance to DNA-methylation agents in cells with defective mismatch repair, the susceptibility to ICR191 observed in these cells suggests that selected drugs can be found to effectively treat tumors with a defective mismatch repair mechanism.

This disparity in the roles of DNA repair in cancer susceptibility and drug resistance, a double-edged sword, poses a challenge to translational research. A better understanding of the roles of DNA repair in disease etiology and treatment could provide valuable information needed for more effective cancer prevention and improved clinical outcome.

REFERENCES