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Forum Editorial

Redox Control of Carcinogenesis and Tumor Biology

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After years of studies, it is well established that alterations of genomic DNA are mainly responsible for carcinogenesis. In a sense, carcinogenesis may be viewed as a "struggle for evolution" in cells. Reactive oxygen and nitrogen species cause DNA damage and modifications, leading to changes in the genomic information. These phenomena are defined as "mutation" and may consist of point mutation, deletion, insertion, or chromosomal translocation. These events may cause activation of oncogenes (proliferation-associated genes) or inactivation of tumor suppressor genes. The latter is basically classified into three categories: caretakers (DNA repair genes), gatekeepers (cell-cycle inhibitors), and apoptosis-associated genes (19).

The caretakers detect structural alterations of genomic DNA and maintain its integrity. It is estimated that ~130,000 damage events occur per day per genome in rats. Fortunately, they are mostly repaired (1). Among the lesions of oxidative DNA damage, 8-hydoxy-2′-deoxyguanosine (8-OHdG) has been most finely studied thus far. 8-OHdG might cause G:C to T:A transversion-type point mutations when present at DNA replication (13). Recently, it was shown that knockout mice of *ogg1* encoding an enzyme to repair 8-OHdG lesions in the genome reveal significantly higher incidence of lung cancer at 1 year and 6 months of age under control conditions (12). This is among the strongest evidence that oxidative DNA damage is intimately associated with carcinogenesis.

On the other hand, free radical reactions have been considered to have little specificity, especially *in vitro,* in contrast to the extremely selective antigen–antibody interactions in immunological reactions. For example, the second-order rate constant for the reaction of hydroxyl radical with guanine is $1.0 \times 10^{10}\, M^{-1}s^{-1}$ (3). Thus, it might be hypothesized that the genome is randomly damaged and that there are no specific "target" genes in Fenton reaction-based carcinogenesis. We doubted this hypothesis because ferric nitrilotriacetate (Fe-NTA)-induced renal cancers are rather homogeneous in histology (8, 10, 17). We used a genetic strategy to investigate whether there is any target gene(s) in this carcinogenesis model. This model was developed in our laboratory 20 years ago and induces the Fenton-like reaction specifically at the brush border membrane of renal proximal tubules. After repeated intraperitoneal administration of Fe-NTA, renal cell carcinoma is observed in >90% of the treated rats.

We scanned the whole genome of Fe-NTA-induced renal cell carcinoma in F_1 hybrid rats in search of allelic loss (imbalance) with microsatellite polymorphic markers. Experiments revealed a significantly elevated frequency of allelic loss (>30%) on rat chromosomes 5 and 8 (15). The presence of common chromosomal areas for allelic loss suggests the presence of a target tumor suppressor gene according to Knudson's "two hit theory" that both the alleles have to be inactivated in the tumor suppressor gene (6). Thus, allelic loss is one of the rate-controlling steps in the process of this inactivation. After several other molecular studies, we concluded that *p15*^{INK4B} *(p15)* and *p16*^{INK4A} *(p16)* tumor suppressor genes were among the major genes at this position. This was the first report that showed the presence of any target gene in the free radical-induced carcinogenesis model (15). The biological significance of this finding is immense because *p16* is associated not only with the retinoblastoma protein pathway as a cyclin-dependent kinase 4 and 6 inhibitor, but also with the p53 pathway via p19^{ARF} and MDM2 (mouse double minute 2) (5, 16). *p19*^{ARF} is an alternatively spliced transcript from the *p16* tumor suppressor gene (2). Indeed, it appears that iron-mediated oxidative damage hits one of the most critical sites of the genome. We later showed that allelic loss of *p16* occurs quite early in carcinogenesis and is gene-specific (4). These results suggest the presence of fragile sites in the genome.

Recently, it has been recognized that oxidative stress induces nonmutational changes to the cells. This plays a role not only in carcinogenesis, but also in tumor biology (18). The main endogenous source of oxidative stress is mitochondria. In this forum on "redox control of carcinogenesis and tumor biology," we have collected five original research communications with special reference to manganese superoxide dismutase. Their significance is fully discussed in the following editorial (9). Furthermore, we have chosen three reviews of hot topics in this area: *Helicobacter pylori*-induced gastric carcinogenesis (11), ultraviolet-induced skin carcinogenesis (7), and chemoprevention by tea polyphenols (14).

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ABBREVIATIONS

Fe-NTA, ferric nitrilotriacetate; 8-OHdG, 8-hydroxy-2′-deoxyguanosine.

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