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Forum Editorial

Mitochondria, Manganese Superoxide Dismutase, and Cancer

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RECENT EVIDENCE has defined new unexpected functions of mitochondria in regulation of cell behavior, and firm connections have now been made between mitochondria and tumorigenesis. Original articles in the present *Antioxidants & Redox Signaling* Forum will link this recent information to the mitochondrial enzyme manganese superoxide dismutase (MnSOD).

MITOCHONDRIA

Each human cell contains several hundred copies of mitochondrial DNA (mt-DNA), which encodes 13 Krebs cycle and respiratory-chain subunits, 22 transfer RNAs, and two ribosomal RNAs (4). The numerous other mitochondrial proteins are encoded by nuclear DNA. The main function of mitochondria is to produce cellular energy and, during this process, acetyl-coenzyme A is passed through the Krebs cycle to generate electrons. These electrons are transferred to the proteins of the respiratory chain in the inner mitochondrial membrane. This generates a proton gradient between the mitochondrial matrix and the intermembrane space, which is used to generate ATP via ATP synthase.

In addition to serving as the main intracellular source of energy of the cell, mitochondria regulate several cellular processes that are linked to apoptosis, which include electron transport and energy metabolism. They are also the storage site for a number of soluble proteins that mediate apoptosis, including cytochrome *c*, certain procaspases, and apoptosis-inducing factor. Mitochondria can activate apoptosis by releasing these factors from their intermembrane space into the cytoplasm, and also by altering the cellular redox (reduction–oxidation) potential (1, 12, 29). During this process, reactive oxygen species (ROS) are generated that can serve as crucial proapoptotic factors.

Mitochondria have been shown to play a role in maintaining cellular redox status by eliminating cytosolic superoxide radicals (7). Cytosolic superoxide scavenging by mitochondria is accomplished by a polarized inner mitochondrial membrane, which is positively charged during respiration. This phenomenon enhances the spontaneous dismutation of superoxide, which diffuses into the mitochondrial intermembrane space because of a localized proton-rich environment. Here, superoxide radicals are protonated to form hydroperoxyl radicals, which can diffuse into mitochondrial matrices and are dismutated by MnSOD. The net superoxide radical consumption in mitochondria creates a gradient for superoxide radicals, which favors diffusion from the cytosolic to the mitochondrial space. Increased MnSOD in mitochondria will thus enhance superoxide radical removal from both mitochondria and the cytosol.

Although energy generation, regulation of apoptosis, and redox regulation are established functions of mitochondria, new functions will probably be identified. In the present Forum, the article by Kim *et al.* (11) provides evidence that mitochondrial redox state is a negative regulator of cell proliferation. Positive regulation of cell growth in nonmalignant mammalian cells is typically characterized by growth factor activation at the cell surface of specific signal transduction pathways that activate crucial transcription factors to regulate genes that are necessary for cell growth. However, the article by Kim *et al.* (11) demonstrates that overexpression of MnSOD in NIH/3T3 fibroblasts via an inducible retroviral vector system led to decreased cell growth due to prolonged cell-cycle transition times in G_1 and S phases. Changes in cell-cycle times were reversible following removal of the inducer, indicating that the changes observed were most likely physiologic in nature. Similar results have been reported with adenoviral transduction of MnSOD cDNA, with the additional finding that higher levels of MnSOD cDNA expression resulted in apoptosis (10). Studies using inducible transfection and adenoviral transduction are of particular significance because previous studies of effects of MnSOD used stable transfection techniques, in which results are more difficult to interpret because of cell adaptations to long-term MnSOD overexpression. As immunogold ultrastructural analysis showed localization of MnSOD-immunoreactive protein in mitochondria in both inducible retroviral transfection and adenoviral transduction systems, it was concluded that altered *mitochondrial* redox state caused by MnSOD overexpression negatively

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regulated cell growth. It was hypothesized that the function of negative regulation of cell growth by mitochondria is protective in nature to prevent cell proliferation at a time when mitochondrial redox state is not optimal to sustain normal cell division. Recent studies in my laboratory have provided additional evidence for this hypothesis because we have demonstrated that addition of a low-molecular-weight mitochondrial antioxidant mitoQ (9) to NIH/3T3 fibroblasts significantly reversed growth inhibition caused by MnSOD overexpression (unpublished observations).

MITOCHONDRIA AND CANCER

The role of mitochondria in cancer has been controversial. Although changes in mitochondrial metabolism (15) and morphology (6) have been described, hypotheses concerning cancer have centered on the effects of nuclear mutations. It has recently been demonstrated that two types of inherited neoplasia syndromes are caused by defects in nuclear genes coding for mitochondrial proteins, *e.g.*, succinic dehydrogenase and fumarase (3).

A number of mutations, deletions, and insertions in mt-DNA have been associated with specific cancers (30). Mt-DNA is particularly susceptible to damage by environmental carcinogens because it contains no introns, has no protective histone or nonhistone proteins, and is exposed continuously to endogenous ROS.

ROS AND MnSOD

Redox reactions, which involve the transfer of electrons or hydrogen atoms from one atom to another, are the major source of superoxide production from oxygen utilization. Superoxide radicals, the product of the one-electron reduction of molecular oxygen, are produced in mitochondria as a result of the imperfect flow of electrons through the electron transport chain. Although superoxide radicals are not considered highly reactive, their toxicity has been clearly demonstrated by the necessity that they be removed for survival of aerobic life. The significance of the unconventional relationship between superoxide reactivity and toxicity was initially recognized by the discovery of superoxide dismutase (SOD), a family of metalloenzymes that defends against superoxide radicals (16). The form of SOD found in mitochondria is MnSOD. The importance of MnSOD for aerobic life was demonstrated by the fact that homozygous MnSOD knockout mice die within 2 weeks after birth (14, 17). These mice exhibit mitochondrial injury because mitochondrial enzymes showed decreased activities and mt-DNA exhibited increased oxidation (18). The critical role of MnSOD may be due to its strategic location in mitochondria and the effectiveness of superoxide radicals in striking critical targets in the respiratory chain.

The main enzymatic function of MnSOD is to convert superoxide anion into hydrogen peroxide, which is subsequently converted to glutathione disulfide and water by glutathione peroxidase in mitochondria. Although a main function of MnSOD is protection against ROS, it is highly likely that MnSOD has physiological functions as well. Addition of hydrogen peroxide to isolated mitochondria caused reversible inhibition of mitochondrial enzymes such as succinic dehydrogenase, and it has been postulated that this mechanism serves to rapidly reduce ROS until other key longer-term biochemical adaptations can occur (21). It has also been demonstrated that mitochondrial oxidants are regulators of cell metabolism, with mitochondrial oxidants having been demonstrated to activate c-Jun N-terminal kinase, resulting in inhibition of the activities of the cytosolic metabolic enzymes glycogen synthase kinase 3β and glycogen synthase (20). It is possible that production of mitochondrial oxidants may thus serve numerous physiologic functions, including regulation of cell division and apoptosis as described below.

MnSOD AND CANCER

It has been repeatedly demonstrated that MnSOD activities are altered (either increased or decreased) in cancer cells when compared with the putative cell of origin (24). This led Oberley and Buettner (23) in 1979 to predict that normalization of MnSOD activities in cancer cells would result in a more normal cell phenotype. Since that time, numerous studies have shown that MnSOD overexpression resulted in inhibition of cell growth both *in vitro* and *in vivo*. For several reasons, this concept remains controversial. First, many enzymes are altered in cancer, so why should this one enzyme be so important? Second, how could an enzyme that could be either increased or decreased lead to the cancer phenotype? Third, what are the mechanism(s) by which MnSOD activities are altered in cancer? Finally, how could a mitochondrial enzyme affect the carcinogenesis process?

Although detailed answers to these questions remain unknown, the original articles in this Forum begin to address these questions. All of these articles study the modulation of MnSOD in *in vitro* or *in vivo* models. However, as discussed previously, the results from these studies should be viewed from the broader perspective of MnSOD regulating mitochondrial redox state, which in turn regulates mitochondrial function.

TUMOR SUPPRESSIVE EFFECTS OF MnSOD OVEREXPRESSION INVOLVES PEROXIDE METABOLISM

The article by Ridnour *et al.* (27) used a stable transfection system to modulate MnSOD in a malignant rat cell line. Interestingly, the authors isolated three transfectants with an increase in MnSOD activity, and one clone had a decrease in MnSOD activity. Regardless, all transfectants showed reductions in *in vitro* and *in vivo* cell growth compared with the parental cells, as well as a reduction in metastatic potential. These transfectants demonstrated variations in glutathione peroxidase and catalase activities; these differences were suggestive of alterations in their abilities to metabolize peroxide when compared with the parental cell line. These studies show that either increased or decreased MnSOD expression will

decrease cell growth, suggesting that altered mitochondrial redox is crucial in regulating cell growth properties of cancer cells. In agreement with these results, our laboratory has published *in vivo* studies in human prostate cancer tissues that demonstrated that MnSOD-immunoreactive protein was low in primary cancer, but elevated in metastatic cancer, in comparison with normal prostate epithelium (25), demonstrating that either high or low levels of MnSOD may be associated with abnormal cell growth. The results in the article by Ridnour *et al.* (27) also demonstrated that analysis of a single antioxidant enzyme was not sufficient to predict the redox state of a cell. Many discrepancies in the literature may be resolved by measuring redox state and activities of all known antioxidant proteins to develop an antioxidant protein profile for each cancer cell type.

MnSOD OVEREXPRESSION HAS BOTH PRO-OXIDANT AND ANTIOXIDANT EFFECTS

The article by Zhong *et al.* (33) used a stable transfection system in a human prostate cancer cell line to demonstrate that MnSOD overexpression altered cell redox state. MnSOD-overexpressing cells showed an increase in sensitivity to the cytotoxicity of buthionine sulfoximine, a glutathione-depleting agent, or vitamin C, but a decrease in sensitivity to sodium selenite. The response of the cells to selenite or vitamin C could be simulated with a SOD mimic, demonstrating that it is the enzymatic function of SOD that regulates the sensitivity of these cells to cytotoxicity. The data demonstrated that overexpression of MnSOD or treatment of cells with a SOD mimic could result in antioxidant or pro-oxidant effects on cells, depending on the presence of other antioxidants or pro-oxidants. These results may reflect the dual nature of MnSOD, acting as an antioxidant by removing superoxide, but also functioning as a pro-oxidant by producing hydrogen peroxide, although it has not been proven that hydrogen peroxide is the reactive species ultimately affecting cell behavior. The peroxide-induced effects described by Ridnour *et al.* (27) and Zhong *et al.* (33) have been confirmed by previous studies that demonstrated that effects of MnSOD overexpression could be reversed by double transfection with cDNAs for glutathione peroxidase (13) or catalase (28).

MnSOD MUST BE TARGETED TO MITOCHONDRIA TO PROTECT AGAINST HYPOXIA/REOXYGENATION-INDUCED CELL DEATH

It has been hypothesized that MnSOD is a unique enzyme with both antioxidant and physiologic roles precisely because it is localized in mitochondria. To determine whether localization was important in regulating the response of human pancreas carcinoma cells to hypoxia/reoxygenation, Hirai *et al.* (8) performed stable transfection studies using MnSOD cDNA with or without a mitochondrial targeting signal to target MnSOD protein to mitochondria or cytoplasm, respectively. Enzyme activity studies showed that both types of transfectants had increased MnSOD activity. Their results showed that hypoxia/reoxygenation caused no increase in nitric oxide, but resulted in increases in ROS, 4-hydroxy-2-nonenal protein adducts, and apoptosis. Authentic MnSOD protected against ROS and 4-hydroxy-2-nonenal protein adduct formation, but MnSOD lacking a mitochondrial targeting signal did not. These results indicated that SOD regulated apoptosis only when it was localized in mitochondria.

MnSOD OVEREXPRESSION REGULATES OXIDATIVE DAMAGE, MITOCHONDRIAL INJURY, AND CELL KINETICS IN A MOUSE SKIN CARCINOGENESIS MODEL

The study by Oberley *et al.* (26) was performed *in vivo* in wild-type or transgenic mice overexpressing MnSOD in a model of chemical carcinogenesis in the skin. A previous study using this model demonstrated that MnSOD overexpression reduced the number of skin papillomas in MnSOD transgenic mice in comparison with wild-type mice (31). The present study demonstrated that skin treated with a single dose of tumor initiator and promoter developed greater oxidative and mitochondrial damage in wild-type skin in comparison with MnSOD transgenic mouse skin. At the same time, analysis of apoptosis and mitosis in skin showed greater indices of both cell birth and cell death in MnSOD transgenic mouse skin in comparison with wild-type mouse skin, indicating that increased mitochondrial MnSOD affected both mitosis and apoptosis. A previous study demonstrated that MnSOD knockout mice in comparison with wild-type mice had equal numbers of papillomas in this skin carcinogenesis model (32), and this unexpected result was reconciled by demonstrating increased cell turnover in MnSOD knockout mice in comparison with wild-type mice, with apoptosis exceeding cell proliferation and thus preventing papilloma formation. These results indicated that either under- or overexpression of MnSOD regulated both cell birth and cell death *in vivo*, presumably because both resulted in alterations in mitochondrial redox state.

PERSPECTIVES

The role of MnSOD in cancer has been controversial. With a greater understanding of mitochondrial function and MnSOD biochemistry, it now seems likely that MnSOD affects mitochondrial redox state, which in turn regulates overall cell behavior. Despite controversies, MnSOD has already been shown to be of great utility in treatment of cancer in experimental animal systems (22). For further progress to be made, at least two requirements must be met: there must be a thorough understanding of how MnSOD is regulated biochemically at all levels [mutations or polymorphisms (19), transcriptional, mRNA stability, translational, and posttranslational modifications] in normal and malignant tissues, and there must be a thorough understanding of mitochondrial biology in normal and malignant tissues. Recent articles have

already described differences in mitochondrial biochemistry in normal versus malignant tissues (2, 5). Studies of the effect of mitochondrial redox state on cell biology are already in progress in many laboratories and should provide important new information about cancer cell biology.

ABBREVIATIONS

MnSOD, manganese-containing superoxide dismutase; mt-DNA, mitochondrial DNA; redox, reduction–oxidation; ROS, reactive oxygen species; SOD, superoxide dismutase.

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