ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 7 & 8, 2006

Forum Editorial

Redox Signaling in Cancer Biology

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ABSTRACT

Over the last three decades, it is has become increasing clear that intracellular signaling pathways are activated via changes in intracellular metabolic oxidation/reduction (redox) reactions involving reactive oxygen species (ROS; *i.e.*, superoxide and hydrogen peroxide). The initial proposals hypothesized that signaling through metabolic oxidation/reduction (redox) reactions involving ROS could contribute to carcinogenesis and progression to malignancy. Strong evidence for this hypothesis was obtained from studies showing that environmental insults (*i.e.*, ionizing radiation) as well as xenobiotics (*i.e.*, polycyclic aromatic hydrocarbons and phorbol esters) capable of inducing steady-state increases in free radical production and ROS could act as both initiators and promoters of carcinogenesis. This Forum is directed at understanding possible redox signaling mechanisms governing cellular radiation response, tumor growth, and response to therapy, as well as the role of nitric oxide in cancer biology. *Antioxid. Redox Signal.* 8, 1249–1252.

Over the last three decades, it is has become increasing clear that intracellular signaling pathways are activated via changes in intracellular metabolic oxidation/reduction (redox) reactions involving reactive oxygen species (ROS; *i.e.*, superoxide and hydrogen peroxide) (1, 2, 4, 6, 21, 22, 24, 28, 29, 32). The initial proposals hypothesized that signaling through metabolic oxidation/reduction (redox) reactions involving ROS could contribute to carcinogenesis and progression to malignancy (2, 6, 21, 22, 24). Strong evidence for this hypothesis was obtained from studies showing that environmental insults (*i.e.*, ionizing radiation) as well as xenobiotics (*i.e.*, polycyclic aromatic hydrocarbons and phorbol esters) capable of inducing steady-state increases in free radical production and ROS could act as both initiators and promoters of carcinogenesis (reviewed in 2, 6, 21, 22, 24, 28, 29). This was thought to occur by increasing mutagenesis, inhibiting differentiation, converting protooncogenes into oncogenes as well as inactivating tumor-suppressor genes, and stimulation of mitogenesis (2, 6, 21, 22, 24, 25, 28, 29, 32).

Further support for a prooxidant environment in cancer cells came from studies showing that in general cancer cells showed altered expression of cellular antioxidants that metabolized ROS, particularly Mn superoxide dismutase and enzyme systems involved in hydroperoxide metabolism, such as catalase (21, 22, 24). In addition, reports suggested that cancer cells produced increased steady-state levels of ROS (particularly hydroperoxides), relative to normal cells, presumably from some metabolic process (5, 29, 34). Furthermore, dietary antioxidants were shown to act as anticarcinogens in a variety of models of malignant transformation (2, 6). These results all provided strong support for the hypothesis that increases in the steady-state levels of free radicals and ROS in mammalian cells could lead to a prooxidant state that was causally involved with malignant transformation (2, 6, 21, 22, 24, 28, 29).

As the body of evidence supporting the involvement of redox reactions in the malignant transformation process was accumulating, a clearer mechanistic understanding of the involvement of redox signaling in normal cellular processes

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emerged. In general, protein kinases were found to be activated and protein phosphatases were found to be inhibited by exposure to oxidants (7, 13, 30, 33, 36). A multitude of transcription factors were discovered to contain redox regulatory sites (primarily cysteine residues), and mutations in these regulatory sites were shown to convert protooncogenes into oncogenes as well as inactivating tumor-suppressor genes (1, 25, 32). Furthermore, cell growth signaling was found to be stimulated by oxidants (33), and growth factors were discovered to stimulate cell division by activating redox-sensitive ROS-mediated signaling pathways thought to involve oxidase enzymes (*i.e.*, NADPH-oxidases) as well as mitochondrial metabolism (4, 10, 18, 19, 33). Finally, increasing steady-state levels of metabolic ROS production by overexpressing NADPH-oxidase enzymes or mutations in genes coding for mitochondrial electron transport chain proteins was shown to increase transformation (14, 31). These findings all support the hypothesis that normal cell-signaling processes involve many redox-sensitive regulatory sites and that these signaling processes can be disrupted by changes in oxidative metabolism that are associated with neoplastic transformation. This has led to the suggestion that cancer could represent a constellation of metabolic and/or genetic diseases in which the common theme is uncoupling of normal cellular processes that govern cell growth and development caused by the inappropriate flow of electrons from metabolic oxidation/reduction reactions to redox-sensitive signal-transduction and gene-expression pathways (29).

In addition to the aforementioned evidence that redox signaling was involved with the process of transformation, evidence emerged that altered metabolic redox states in cancer cells could be exploited to kill cancer cells selectively, relative to normal cells. Initially it was shown that the toxicity of chemotherapeutic agents as well as radiation toward cancer cells could be enhanced by agents that inhibited the function of thiol-dependent (*i.e.*, glutathione and thioredoxin) antioxidant detoxification systems involved with resistance to therapy (20, 39). It was also hypothesized that treating patients with exogenous thiol antioxidants could selectively protect normal tissues from oxidative damage during chemotherapy and radiation therapy (11, 37, 38) and improve outcome. More recently, it has been proposed that treating cancer cells with vectors causing the overexpression of MnSOD and catalase could inhibit tumor cell growth, presumably by disrupting redox signaling involved with cell division (23) as well as protecting normal tissues from therapeutic intervention (12). Finally, it has been shown that cancer cells are more susceptible than normal cells to glucose deprivation–induced metabolic oxidative stress (5, 29). This was hypothesized to be the result of increased glucose metabolism in cancer cells to obtain reducing equivalents to compensate for increased steady-state levels of hydroperoxide production by defective mitochondrial oxidative metabolism (5, 29). Furthermore, inhibitors of glucose and hydroperoxide metabolism have been suggested to enhance metabolic oxidative stress selectively in cancer cells (relative to normal cells), leading to both radio- and chemosensitization (3, 16). Taken together, the current evidence presented in this overview demonstrates that disruptions in metabolic redox signaling contribute to both the genesis and maintenance of the malignant phenotype, as well as potentially providing a biochemical rationale for selective killing of cancer cells, relative to normal cells. With this background in mind, the following contributions were chosen for this Forum Issue to highlight recent developments in the field.

The original research contributions fall into two main categories relevant to redox signaling and cancer biology. The first group is directed at understanding possible mechanisms governing cellular radiation response. In Pandey *et al.* (26), the effects of low- and high-dose radiation on mitochondrial membrane potential and protein import were found to be quite different; with low-dose radiation stimulating and high-dose radiation inhibiting protein import and membrane potential in normal human fibroblasts. The authors suggest that these differential effects on mitochondrial metabolic state and subsequent redox signaling may have significant physiologic implications after high and low doses of radiation. Cook *et al.* (8) studied the baseline and radiation-induced gene-expression profiles of murine head and neck cancer cells exposed *in vitro* and *in vivo* and found that the gene-expression profiles from the same tumor cells grown under different metabolic conditions differed significantly, as did the expression changes induced by radiation exposure. They also found that the expression of a significant number of genes governing metabolic redox responses were among those affected by ionizing radiation. These results provide further support for the hypothesis that exposure of cancer cells to ionizing radiation causes changes in gene expression and metabolic redox signaling that could contribute to radiation responses. This work also highlights the need to control initial environmental conditions carefully before making conclusions about the relative importance of gene-expression changes to biologic responses. In the final article studying radiation effects, Kalen *et al.* (15) found that prolonged stable overexpression of the mitochondrial form of the superoxide dismutase enzyme (MnSOD) in human head and neck cancer cells enhanced radiation-induced G_2 accumulation and radioresistance. Because MnSOD is an enzyme thought to modify intracellular redox signaling and cell-cycle progression, these results support the hypothesis that mitochondrially derived metabolic redox signaling can modify radiation responses by altering cell-cycle progression and the G_2-checkpoint pathway.

The second group of original contributions is directed at elucidating redox signaling pathways that affect cancer cell responses relevant to inhibiting tumor growth and cancer therapy. By using site-directed mutagenesis of the active site, Zhang *et al.* (40) determined that that the growth-suppressive effects of overexpressing MnSOD in transformed cells is caused by the enzymatic activity of the protein. These results support the idea that increasing the dismutation of mitochondrial superoxide alters redox signaling in cancer cells that can result in growth suppression. In addition, it suggests that either steady-state levels of mitochondrial superoxide may be involved in maintaining cancer cell growth or hydrogen peroxide (the product of the dismutation reaction) may be involved in inhibiting tumor cell growth. In the article by Dasgupta *et al.* (9), they show that stable overexpression of MnSOD protects human fibrosarcoma cells from tumor necrosis factor–mediated apoptosis. Based on these results, they suggest that increasing steady-state concentrations of

hydrogen peroxide, by overexpressing MnSOD, inactivate redox-sensitive signaling leading to caspase activation (9). These two articles (Zhang *et al.* and Dasgupta *et al.*) coupled with the Kalen *et al*. article also bring up the important point that MnSOD overexpression can have beneficial as well as deleterious effects on cell growth when developing cancer therapeutic strategies. One possible explanation for this apparent paradox is likely to involve the overall redox balance in the cancer cells at the time of treatment. Based on these observations, it is tempting to speculate that a key determinant of outcome in cancer cells overexpressing MnSOD may be the expression of hydrogen peroxide scavenging systems (*i.e.*, catalase, glutathione peroxidases, and/or peroxiredoxins); however, this awaits further verification.

Luo *et al.* (17) show that inhibition of MnSOD, CuZnSOD, and catalase activities can be accomplished by treating cells with singlet oxygen derived from photodynamic therapy. These results suggest that photodynamic therapy can be used in conjunction with other anticancer agents that increase superoxide and hydrogen peroxide production to improve tumor cell killing in combined-modality cancer therapy protocols. The final article in this group by Tome *et al.* (35) shows that overexpression of the first enzyme in the pentose phosphate cycle (where NADPH is regenerated from NADP+) sensitizes murine thymic lymphoma cells to cell killing mediated by several standard chemotherapeutic agents. These results encourage speculation that excess reducing equivalents, in the form of NADPH, can sensitize cancer cells to redox signaling, resulting in apoptosis (possibly through NADPH-dependent oxidase enzymes) during combined-modality chemotherapy.

The last forum contribution by Ridnour *et al.* (27) reviews and highlights the exciting field of nitric oxide–mediated redox signaling (in addition to ROS-mediated signaling) and its relevance to both cytoprotective and cytotoxic responses in cancer biology. Finally, the guest editors thank all the authors for their excellent and provocative contributions to this forum on redox signaling and cancer biology. We also hope that the readers of this issue will become inspired to make scientific contributions from their own laboratories to this growing field of study.

ACKNOWLEDGMENTS

We thank Laura Hefley and Teresa Sanello for their administrative assistance in manuscript preparation. D.G. was supported by the intramural program at the NIH/NCI. D.R.S. was supported in part by DOE DE-FG02–05ER64050, DE-FG02–03ER63634, NIH R01-CA100045, P01-CA66081, and P30-CA086862.

ABBREVIATIONS

CuZnSOD, copper zinc superoxide dismutase; MnSOD, manganese superoxide dismutase; NADPH/NADP+, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species.

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Date of first submission to ARS Central, January 18, 2005; date of acceptance, January 22, 2006.

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