CLINICAL IMPLICATIONS OF BASIC RESEARCH

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The Promise and Perils of Antioxidants for Cancer Patients

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Reactive oxygen species (ROS) have been proposed to both accelerate and delay cancer initiation and progression. These conflicting outcomes may be explained by the multiple roles that ROS play during the evolution of cancer cells.

ROS can promote cancer by oxidizing specific intracellular chemical moieties, resulting in genetic mutations and the activation of biochemical pathways that stimulate proliferation and neoplastic transformation.[1] These tumorigenic properties of ROS have prompted the evaluation of dietary antioxidants as potential preventive and therapeutic agents in animal models and humans. Although some early preclinical studies supported this concept, dietary antioxidants have consistently failed to reduce the incidence of carcinoma in prospective human clinical trials. Rather, some studies have even suggested a harmful effect of antioxidants in persons at risk for cancer.[2] A recent study by Sayin and colleagues[3] in genetically engineered mouse models that mimic human early non–small-cell lung cancer has confirmed that the antioxidants *N*-acetylcysteine and vitamin E actually increase cancer burden and mortality in a dose-dependent manner. Why have antioxidants consistently failed to reduce carcinoma burden in experimental models and in clinical trials, refuting the ROS tumor-promoting hypothesis? Recent mechanistic insights into ROS biology may provide explanations for the failure of dietary antioxidants in patients.

ROS play important roles in normal cellular physiology, in which low levels of ROS are generated from molecular oxygen through mitochondrial respiration and a family of membrane-bound NADPH oxidases (NOXs) (Fig. 1). These ROS oxidize spatially colocated proteins to activate multiple signaling pathways that regulate cellular viability, proliferation, differentiation, and metabolic adaptation.[1] Cancer cells increase their production of mitochondrial ROS to further stimulate neoplastic transformation.[4] However, the response of cells to ROS is biphasic: high levels of ROS are toxic. In particular, the ROS hydrogen peroxide (H_2O_2) can diffuse to distant parts of the cell and cause oxidative damage that results in cell-cycle arrest and cell death. Indeed, the therapeutic effect of ionizing radiation and many common chemotherapeutic agents in the treatment of cancer depends on the cytotoxic action of ROS.[4]

To compensate for the higher levels of intrinsic ROS, cancer cells have evolved adaptive mechanisms that increase the antioxidant properties of cells and thereby maintain pools of reduced glutathione and thioredoxin. This permits cancer cells to use ROS to activate proximal signaling pathways that stimulate neoplastic cell behavior, while simultaneously and rapidly repairing the collateral oxidative damage caused by ROS in bystander macromolecules that would otherwise induce the death or senescence of cancer cells.

On the basis of this current understanding of redox biology of cancer cells, we propose two potential antioxidant therapeutic approaches to prevent or treat cancer. First, therapies that directly inhibit the production of mitochondrial- and NOX-derived ROS, or that scavenge ROS at these sites, will be more effective than the dietary antioxidants, because the latter poorly access the mitochondrial-localized pools of ROS required for signaling. Indeed, mitochondrial-targeted antioxidants are more potent inhibitors of tumor-cell proliferation than the same antioxidants that concentrate in the cytosol.[5] Thus, the failure of dietary antioxidants in clinical trials might be due to their inability to scavenge ROS at the site of production. By extension, the tumor-accelerating properties of dietary antioxidants may reflect the stimulation of oncogenic proteins that are attenuated by distant ROS and may also reflect the inactivation of certain tumor-suppressor proteins, including p53, that are conversely activated by ROS.[3]

Second, it is possible that there is a synthetic lethal strategy that disables the antioxidants within cancer cells that correct the oxidative damage caused by diffused H_2O_2, thus permitting cellu-

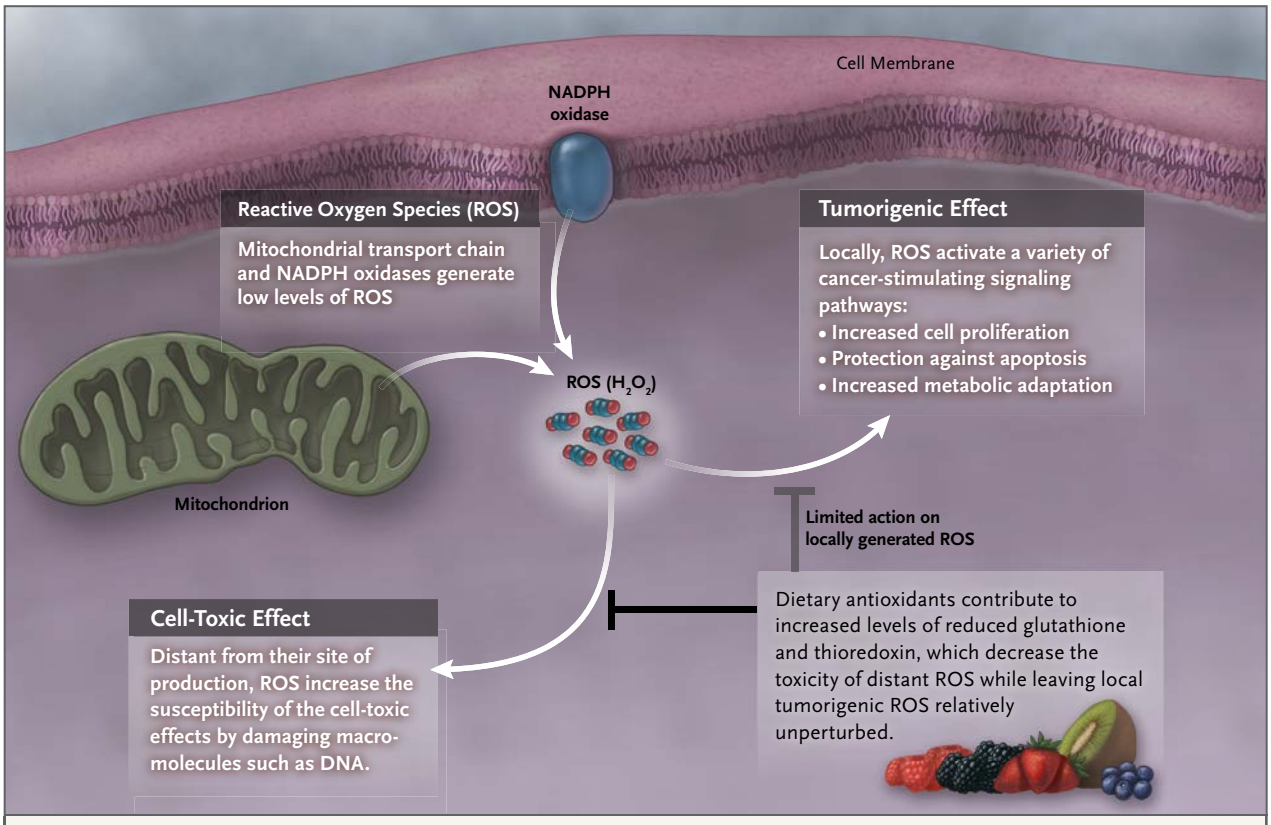

Figure 1. Effect of Dietary Antioxidants on Reactive Oxygen Species (ROS).

ROS are generated at low levels by the mitochondrial electron transport chain and by NADPH oxidases localized to the plasma membrane and other organelle membranes. ROS generated at these sites specifically oxidize certain spatially colocated proteins to activate a variety of cancer-stimulating signaling pathways. Distant from the mitochondria and NADPH oxidases, ROS nonspecifically damage macromolecules (DNA, RNA, lipids, and proteins) and are toxic to both normal and cancer cells. High levels of ROS introduced into cells (e.g., through ionizing radiation and chemotherapy) are toxic to cells in a similar manner. As compared with normal cells, neoplastic cells generate more ROS, requiring them to have a greater antioxidant capacity that reduces distant ROS damage while simultaneously allowing localized ROS signaling that promotes cell proliferation and survival. Dietary antioxidants effectively contribute to the increased pool of reduced glutathione and thioredoxin and thereby reduce the toxicity of distant cellular ROS while leaving the locally generated and tumorigenic ROS relatively unperturbed.

lar arrest or death.[4] Indeed, genetic or pharmacologic inhibition of antioxidant proteins decreases tumor burden in experimental mouse models of lung and pancreatic cancer.[4] A challenge for this approach is to identify antioxidant proteins and pathways that are selectively used by cancer cells and not by normal cells, and in particular stem cells, to maintain redox balance. We propose that antioxidant profiling of tumor cells and their adjacent normal cells may decipher the nodes of antioxidant pathways that are enriched in tumor cells as possible therapeutic targets, providing a tailored strategy to decrease cancer incidence and improve treatment outcomes for patients.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Finkel T. Signal transduction by reactive oxygen species. J Cell Biol 2011;194:7-15.
2. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029-35.
3. Sayin VI, Ibrahim MX, Larsson E, Nilsson JA, Lindahl P, Bergo MO. Antioxidants accelerate lung cancer progression in mice. Sci Transl Med 2014;6(221):221ra15.
4. Gorrini C, Harris IS, Mak TW. Modulation of oxidative stress as an anticancer strategy. Nat Rev Drug Discov 2013;12:931-47.
5. Weinberg F, Hamanaka R, Wheaton WW, et al. Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. Proc Natl Acad Sci U S A 2010;107:8788-93.

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