ROS to the rescue

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OVERPRODUCTION OF REACTIVE OXYGEN SPECIES (ROS) in biological systems has been associated with the initiation or aggravation of diverse pathological states (14, 19). The presumed mechanism is through the ability of ROS to induce biochemical alterations in macromolecules such as DNA, lipids, and proteins (4, 14, 17). It has been known for some time that ROS, produced physiologically by leukocytes and macrophages as a bactericidal mechanism of host defense, can also damage surrounding tissue. These effects and the cell damage caused by exogenously applied oxidants led to emphasis on the toxic effects of ROS. However, it is becoming increasingly evident that ROS also serve as physiological intracellular signaling molecules (9, 15) because they can, even at low concentrations, activate transcription factors, such as NF-κB, and alter mitogenic signals that affect cell growth, differentiation, and other cellular responses (9, 12). Milla et al., in one of the current articles in focus (Ref. 10, see p. L706 in this issue), take this concept a step further and cast ROS in a protective role where they reduced tissue damage and organ dysfunction in a model of lung inflammation (10). According to their interpretation, oxidants can control inflammation by inducing apoptosis of lymphocytic T cells, thereby decreasing production of proinflammatory cytokines. They postulate a balance between inflammation-mediated oxidative damage to tissues and oxidant-induced protective mechanisms as the most desirable state.

The immunologic model used by Milla et al. (10) is that of bone marrow transplant, following standard clinical procedures of irradiation and introduction of donor T cells at the time of transplant. The lung is an appropriate focus for this study since it is a target organ of the graft-vs.-host reaction in bone marrow transplant (11). Damage to the lung after bone marrow transplantation could occur either as a result of irradiation-induced oxidant injury or from proinflammatory cytokines released by T lymphocytes derived from the donor bone marrow graft. The T cells may attack tissues of the host that are recognized as foreign (8). Milla et al. (10) show that these pathways interact. Thus, whereas the inhibition of radical generation reduces oxidative damage and cellular apoptosis, it also decreases apoptosis in T lymphocytes, resulting in an exaggerated and detrimental immune response.

NADPH oxidase is a major source of ROS associated with oxidative stress in the lung. This enzyme complex is found in endothelium and other lung cells but is expressed at especially high levels in neutrophils, monocytes, and alveolar macrophages. Cell stimulation during microbial attack or other insults results in the translocation of the cytosolic components of NADPH oxidase to the cell membrane where they assemble with the membrane components to form an electron transfer system that catalyzes the reduction of molecular oxygen to superoxide anion (O2−) while oxidizing NADPH. Increased O2 utilization and increased O2− production are the major characteristics of the “oxidative burst” that results from NADPH oxidase activation. O2− is converted to hydrogen peroxide (H2O2) in a reaction catalyzed by superoxide dismutases (1, 16). Oxidants are also produced by enzymes contained in certain intracellular granules. Azurophilic granules release myeloperoxidase (MPO) that, upon neutrophilic activation, catalyzes a reaction between H2O2 and chloride to produce hypochlorous acid, a highly potent oxidant (5). A similar enzyme, eosinophil peroxidase, is released from eosinophilic granules and results in production of HOBr (13).

These oxidants have an important role in lung inflammation. T lymphocytes, mast cells, and other cells released by bone marrow in noninfectious inflammatory disorders are recruited to the lung alveoli. Activation of these cells results in the release of inflammatory cytokines and chemokines such as TNF-α, IFN-γ, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-α, which induce airway inflammation characterized by apoptosis, pulmonary edema, and necrosis (2, 3). T lymphocytes lodged in inflamed airways appear to be resistant to apoptosis, and their persistence is a major contributor to lung injury. Thus an agent capable of promoting T cell apoptosis could be beneficial in this experimental condition. Milla et al. (10) show that ROS can play the role of T cell apoptosis promoting agent. The evidence for this effect is the reduced propidium iodide and annexin V antibody staining in cells of the bronchoalveolar lavage fluid (BALF) of MPO−/− mice where oxidant generation after bone marrow transplant presumably was lower than that of wild-type mice.

MPO and associated oxidants convert nitrates and peroxides to nitrating agents for lipids and proteins. Milla et al. (10) show that protein nitrotyrosine formation is decreased in MPO−/− mice compatible with decreased oxidative/nitrosative stress. On the other hand, MPO−/− mice had increased alveolar epithelial type II cell injury and death as well as increased T cell-dependent inflammatory response, as indicated by elevated levels of TNF-α and MCP-1 in the BALF. The implication is that the possible beneficial reduction in oxidative damage to cells by absence of MPO-derived oxidants is overcome by the increased immune response. The results further imply that oxidants have an important role in T cell apoptosis but that nonoxidant mechanisms play the greater role in alveolar type II cell injury.

Why does the absence of MPO result in increased inflammation? Milla et al. (10) show that a possible mechanism is decreased apoptosis of T cells and macrophages. The premise is that these inflammatory cells are normally “controlled” by the conflagration of inflammation, but in the absence of MPO, have increased survival. That such enhanced inflammation is also observed when a major source of ROS is compromised, as in NADPH-oxidase gene-targeted mice, is compatible with an important role for ROS-induced apoptosis in controlling injury related to inflammation (18). Thus ROS and other oxidants can, by reducing the number of inflammatory cells, control the extent of tissue damage and lung dysfunction (6, 7, 18).
Although the experimental model studied by Milla et al. (10) provides interesting insights into the role of oxidant/antioxidant balance in disease, the application of the findings may be limited to bone marrow transplant cases where excessive numbers of T cells are a major contributor to pathophysiology. A possible complicating factor for interpretation of the results is the role of antioxidant defenses in these mice. Antioxidant defenses may be altered in the gene-targeted mice and also by the irradiation associated with the bone marrow transplantation protocol. Despite these limitations, the results raise interesting possibilities in terms of therapy of inflammatory disorders. Because optimal levels of ROS induce apoptosis of T cells and can modify the inflammatory response at otherwise subtoxic concentrations, the controlled use of ROS represents a possible therapeutic tool against inflammatory diseases. Of course, the challenge would be to discover and maintain the appropriate level of ROS.

REFERENCES