

Introduction: Reactive Oxygen Species Special Feature

Joan Selverstone Valentine* and Edith Butler Gralla

Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569

Dioxygen is a highly important, yet toxic, molecule that reacts *in vivo* to produce reactive oxygen species such as superoxide, peroxides, hydroxyl radicals, and other related species. Those species play important roles in healthy organisms, and they are implicated in aging and a wide range of disease processes as well. The contents of this Special Feature on Reactive Oxygen Species in Chemistry and Biology represents a sampling of the excellent work that is being carried out at this important interface of chemistry and biology by using a wide range of chemical, kinetic, spectroscopic, and biological approaches. The authors come from several different fields and use a wide diversity of techniques and experimental systems; nevertheless, their studies all relate to the fundamental chemical reactivity of dioxygen and species derived from it.

Starting with the most chemical example, reactive oxygen species frequently react by concerted proton-electron transfer (CPET) mechanisms in chemistry and biology. Markle *et al.* (1) report on a detailed kinetic study of oxidations of a series of phenol-imidazole compounds to give phenoxyl radicals, which helps to define the basic principles of CPET.

Metalloenzymes that catalyze reactions of dioxygen frequently generate their own classes of enzyme-bound reactive oxygen species. In the case of cytochrome P450 enzymes, these intermediates are short-lived and highly reactive iron-oxo species that are difficult to observe directly. Newcomb *et al.* (2) have succeeded in characterizing and report here on the iron(IV) oxo derivative from the P450 enzyme CYP119 by using x-ray absorption spectroscopy.

Small-molecule antioxidants are the subject of many investigations because of their potential medical relevance; the article by Vaz and Augusto (3) is a detailed characterization of some cellular reactions of the molecule Tempol and its ability to inhibit myeloperoxidase-mediated protein nitration.

Redox-active cysteine side chains on proteins are frequently the targets of reaction with reactive oxygen species and may play regulatory roles in addition to being susceptible to damage. Leichert *et al.* (4) report on the development and use of a new and powerful method, termed OxICAT, to identify and quantitate free and bound thiols in cells under different conditions. The application of these techniques to *Escherichia coli* resulted in the identification of different groups of thiol-bearing proteins whose status is changed by hydrogen peroxide or hypochlorite treatment.

Peroxiredoxins are widespread and important enzymes that decompose organic peroxides and hydrogen peroxide, but the mechanism and kinetic parameters have been difficult to determine. Parsonage *et al.* (5), using a newly refined assay method, including genetically engineered components, were successful in measuring reaction rates with different substrates and refining our understanding of these important defensive and regulatory enzymes.

The articles by Castello *et al.* (6) and Raffaghello *et al.* (7) are the most biological and involve whole organism regulatory pathways that direct the responses to hypoxia and oxidative stress, respectively.

Yeast have two versions of the cytochrome *c* oxidase (CCO) subunit Cox V that are differentially regulated by dioxygen tension: Cox Va is expressed aerobically, whereas Cox Vb is turned

on when dioxygen levels drop. Castello *et al.* (6) report that CCO is able to make nitric oxide from nitrite. Their article shows the surprising result that the hypoxic version of CCO, with Cox Vb, is a much more effective producer of nitric oxide from nitrite, and it presents evidence that the nitric oxide generated functions as a signal to turn on expression of various hypoxic genes.

Raffaghello *et al.* (7) have focused on the role of caloric restriction and the stress response in aging, and they are interested in how life span is affected by genetic manipulation of key regulatory pathways. Caloric restriction is one of the few reliable methods to increase life span in a wide variety of organisms. One of the reasons it works is that a variety of stress resistance pathways are activated when nutrients are limited. In the present work, Raffaghello *et al.* report on their efforts to use short-term starvation to induce a stress-resistant state that renders organisms more resistant to chemicals such as anticancer drugs. Their results indicate that this treatment works in yeast and to some extent in mice. Although it may be controversial, the goal is to increase effectiveness of cancer therapeutics. Because cancer cells are less responsive to growth-regulating signals they are likely to remain sensitive to the treatment after starvation, whereas normal cells will increase their resistance to the drug.

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*To whom correspondence should be addressed. E-mail: jsv@chem.ucla.edu.

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